THE DIAGNOSIS OF DIABETES WITH SPECIAL REFERENCE TO THE INTRAVENOUS GLUCOSE TOLERANCE TEST

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Summary

This study is an examination of the purpose, development and technique of the diagnosis of diabetes mellitus.

In recent years the definition of this disorder has relied heavily on the results of diagnostic tests, especially the glucose tolerance test (GTT) in one of its forms. By the use of such a test individuals may be graded into diabetics, non-diabetics and a substantial intermediate group often called diabetic "suspects". There is no obvious dividing line between these three groups and any precise divisions are therefore arbitrary.

It is here shown that the "suspect" group is not an artefact caused entirely by temporary physiological variables or by vagaries in the tests themselves, but is rightly so named, many of its members sooner or later developing clinical diabetes.

Evidence is presented from the literature to show that prompt and adequate treatment of early diabetes - even sometimes when still at the "suspect" stage - can prevent, delay or ameliorate many of the histopathological accompaniments of the disease. In spite of some contrary opinions on this matter it would seem, therefore, that precise and early diagnosis is both desirable and important.

The development of the GTT is traced and variations in its technique and interpretation are discussed. Of the different types the intravenous GTT is subject to least physiological variability

and is capable of the most accurate interpretation. At the present time it is thought that glucose disposal during an intravenous GTT is best expressed by assuming a simple exponential relationship between blood glucose and the time after glucose injection, at least during part of the test. This relationship is represented by a straight line fitted to blood glucose points plotted against time on semilogarithmic graph paper. The slope of such a line is termed the "k" value and represents the rate of fall of blood glucose if a simple exponential relationship obtains. By a method of mathematical analysis this assumption is shown to be roughly correct and adequate for practical purposes but it is suggested that a more complex relationship probably exists, even during that part of the test when cell metabolism is the chief factor in glucose disposal. If this relationship could be determined it might provide a more accurate guide to the actual efficiency of glucose metabolism.

It is shown, on both theoretical and practical grounds, that the use of "total" blood glucose (i.e. the observed level) is to be preferred to "excess" blood glucose (i.e. the difference between the observed and the original fasting level) in the calculation of "k".

Suggestions are also made for the use of a simpler intravenous GTT involving the collection of blood samples only at the 20th, 40th and 60th minutes after glucose injection instead of the more frequent samples usually taken. Allowing for all the minor physiological and technical variables to which the test is subject it is claimed that

the results of the simpler test are within acceptable confidence limits.

Using the simpler test a number of known diabetics and non-diabetics have been studied to show the ranges of "k" values for each group. The diabetic and non-diabetic ranges overlap to some extent and possible explanations for this overlap are discussed.

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Glucose injections and the collection of capillary blood samples for all intravenous glucose tolerance tests were carried out by the author personally. Blood glucose estimations were carried out in the hospital laboratory jointly by the author and by Mr. A. Ogilvie, Senior Laboratory Technician, Adelaide Hospital. Oral glucose tolerance tests were performed as routine procedures in the investigation of hospital patients. Blood and urine samples for these tests were collected by the junior house officers concerned and blood sugar estimations were carried out in the hospital laboratory by various members of the laboratory staff.

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Explanation of Terms: Blood sugar and Blood glucose

It is difficult to maintain both clarity and accuracy with these terms when referring extensively to the work of other authors. Although the key reducing substance contained in the blood of diabetic subjects was recognised as glucose long ago (Chevreul 1815) glucose-specific estimation techniques have only recently been developed as routine laboratory procedures. (Teller 1956).

Earlier non-specific methods for blood sugar estimation (still widely used) measure, in addition to glucose, a number of other reducing substances collectively termed "saccharoids" by Benedict (1931). The quantity of saccharoids estimated by these methods differs according to the particular method used and varies from individual to individual or even in the same individual at different times. Moreover their blood level is not in a constant ratio to that of glucose.

However, in spite of the inherent inaccuracies of such methods it remains true that glucose forms the bulk of blood reducing substances and that fluctuations in the level of blood reducing substances mainly reflects fluctuations in the level of blood glucose. Certainly many earlier writers have used the term, "blood sugar", as if it were equivalent to "blood glucose". In the majority of practical situations the distinction is of little importance although in the discussion of exact biochemical processes the terms used must likewise be exact.

With these considerations in mind, therefore, those terms are used in this thesis as follows:-

Blood glucose - Glucose specifically

Blood sugar - Glucose plus (varying amounts of) saccharoids. When general statements are made combining the views of two or more authors, one speaking of "blood glucose" and another speaking of "blood sugar" (as defined above) the term "blood sugar" is used to cover both meanings.

Terms also used:-

Hypo- or hyper-glycaemia - These refer to the level of blood sugar.

Glycosuria - Sugar in the urine

Glucosuria - Glucose in the urine

"Total" (see section on the Intravenous glucose tolerance test) - The observed level of blood sugar or blood glucose

"Excess" (see IVGTT) - The difference between the observed level of blood sugar or blood glucose and the initial fasting level (or some other level as explained in detail in the text). This term is referred to by some authors as the "increment".

A number of other terms are used and explained in the appropriate context.

INTRODUCTION

Diabetes Mellitus is a disease which is ill understood but frequently diagnosed. To the lay mind it still conjures up the image of a serious and intractable illness. This attitude is, however, changing with the advent of modern drug therapy and the increasing appreciation that diabetic-like biochemical disturbances may be mild or transient and in many cases - especially when the onset is in later life - quite compatible with a normal life span.

So frequently do diabetic-like biochemical disturbances occur, in fact, and in such a wide variety of clinical states that diabetes has come to be regarded by many observers more as a symptom than a disease. With this trend has been the inclination in some circles to regard the diabetic tendency - particularly if revealed only by some specialized diagnostic procedure - as of relatively small importance. As a result older concepts of the disorder have come under scrutiny, the object being not only to establish more precisely the fundamental nature of the disease itself but also to discover the long term aspects regarding prognosis and treatment.

The diagnosis of diabetes is closely connected with both these matters. Developments in diagnostic techniques have paralleled advances in knowledge of the underlying disorder and - more so perhaps than with any other disease - form the basis for its definition. Also the whole rationale of diagnosis - the purpose and usefulness of it in the frequently diagnosed sub-clinical forms of

diabetes at least - rests heavily on the outcome of long term studies currently in progress. Can diagnosis at the stage before clinical onset make any difference to the eventual outcome? Does early treatment help?

The purpose of the present study is to examine some of these points. More especially, the mathematical and practical aspects of the intravenous glucose tolerance test (IVGTT) are discussed in detail in order to determine:-

1. The correct form of exponential relationship between the blood glucose and the time after glucose injection which most closely represents the fall of blood glucose during an IVGTT;

2. The most appropriate section of the IVGTT blood glucose curve to be used as an index of the efficiency of carbohydrate metabolism;

3. A simpler test of comparable accuracy to the usual IVGTT procedure using only a few selected blood glucose readings and

4. The range of normality and abnormality for the IVGTT to be used both for the diagnosis and the definition of diabetes.

DEFINITION

Historical and general

Up to fairly recent years the term "diabetes" stood for a specific disease entity with definite signs and symptoms. As such it was known to the ancient world, both in the East (Bose 1907) and the West. Aretaeus the Cappadocian, in the early part of the second century A.D., describes it as "a melting down of the flesh and limbs into urine (with) thirst unquenchable, disproportionate to the amount of urine, nausea and restlessness and (the patient will) at no great time expire". (Adams 1856). The disorder was , however, ill understood and the same writer observes that "if anyone is bitten by the dipsos (a type of viper) the infection induced by the wound is (also) of this nature." This symptomatic approach to diabetes was maintained until the present century. Then, with increasing comprehension of the biochemical disturbances involved, the emphasis shifted away from the merely clinical and a later definition speaks of diabetes as "a chronic hereditary disease, characterised by an increase of glucose in the blood, and the excretion of glucose in the urine." (Joslin 1959a).

While, however, this description is adequate for a florid example of the disease it is unsatisfactory on at least three counts:-

(1) Such a definition excludes many individuals who, in spite of raised blood glucose levels and markedly reduced glucose tolerance, have no glycosuria. (It should be noted here that very small quantities -

1 - 15 mg. per 100 ml - of glucose are almost invariably detectable in the urine even in normal subjects (Bernard and Ginsberg 1965, Fine 1965). Throughout this study, therefore, unless contrary indication is given, the term "glycosuria" refers to increased quantities of glucose or sugar in the urine, such as are capable of detection by simple routine side-room methods, e.g. using Benedict's solution or "clinitest" tablets, that is, a minimum of about 50 mg. per 100 ml.)

(2) It fails altogether to take account of the specific histological changes which occur, it seems, sooner or later in all diabetics, sometimes even at a stage when the biochemical disturbance is so slight that it has to be sought for by special tests.

(3) It has been increasingly recognised that although in the majority of diabetics no obvious primary cause exists, apparently identical biochemical disturbances - and occasionally even histological abnormalities (Lawrence 1948, Becker 1952) - may occur as temporary phenomena in a great variety of aetiologically unrelated conditions, all of which constitute some form of stress to the individual concerned. Whether these states of temporary metabolic disturbance should be called diabetes is debatable but many do, in fact, progress to florid diabetes if allowed to persist unchecked.

In the light of these objections older views of a clear cut disease entity have been replaced by the concept of a much more ill-defined disorder, possibly representing the final common pathway of a number of different pathological processes. In an attempt at comprehensiveness Crombie (1964) refers to diabetes as a syndrome

comprising a constellation of abnormalities, biochemical and histological, of as yet unknown aetiology and arising in the course of a number of different conditions.

However, some more detailed mention must be made of the particular biochemical and histological changes to be expected. Lozner et al. (1941) offered their definition of diabetes in two parts, (a) metabolically - a state of subnormal maximum attainable carbohydrate metabolism and (b) clinically - by the known signs and symptoms.

Lundbaek (1962) also gives a double definition: Diabetes mellitus - a chronic disease with reduced glucose tolerance in patients not suffering from disease of the pancreas or from acromegaly, Cushing's disease or phaeochromocytoma. Diabetic aberration - any other condition with transitory or permanent reduction of glucose tolerance.

Presenting features of diabetes

None of these definitions is entirely satisfactory. In practice the two main aspects of the disease are (a) the biochemical disturbance, manifested most strikingly and conveniently by a diminished metabolic ability to handle carbohydrate and (b) various histo-pathological abnormalities characterised particularly by a specific micro-angiopathy. Certainly, definite symptoms and signs (the criteria for the majority of specific diseases) are only found in the minority of diabetics (Sharp et al. 1964).

Now although the typical biochemical disturbance of diabetes is

often present in overt or latent form without any apparent specific histological changes, the reverse is quite exceptional. Several examples of "diabetic" lesions occurring in allegedly non-diabetic individuals have been reported in the literature (Newburger and Peters, 1939, Siegal and Allen 1941, Horn and Smetana 1942, Laipply et al. 1944, Dana and Zubroid 1954). Examination of these papers shows, however, that diabetes has usually been excluded chiefly or entirely on negative grounds and often retrospectively at autopsy in subjects where diabetes had not been suspected nor looked for carefully during life. Bell (1950) states that in his two examples diabetes was "definitely excluded" but no clinical details are given to support this claim.

The best documented report is by Moore and Frew (1965) who published their detailed histological findings in the amputated legs of 52 subjects suffering from extensive peripheral vascular disease. All had normal GTT's. In three cases, however, there was typical "diabetic" microangiopathy in the skin and subcutaneous tissues. Apart from these, certain pre-diabetics - that is, persons in the months or years preceding the development of impaired glucose tolerance - sometimes show diabetic-like changes in the capillaries of the ear lobe and renal glomeruli but these are said to be somewhat different from true diabetic micro-angiopathy (Camerini-Davalos et al. 1963).

If, therefore, we would seek a common denominator in all diabetics, the almost invariable biochemical disturbance is clearly more satisfactory than either histological changes or clinical symptoms.

There are many altered biochemical processes in diabetes which are currently under investigation and new diagnostic tests may well emerge before long. For over a hundred years, however, diminished metabolic ability to handle carbohydrate has been the most convenient test and is still the technique usually employed.

Arbitrary standards

Descriptions of the salient features of diabetes may be found in any standard textbook of medicine and are sufficient definition for the clear cut case. In those individuals, however, where the diagnosis is less obvious, some form of glucose tolerance test has come to be the cardinal diagnostic tool and by implication the results of such a test provide the most important definitive boundary mark between diabetes and normality. On the basis of glucose tolerance tests many workers have proposed standards to be used as criteria of normality or abnormality (Exton and Rose 1934, Mosenthal and Barry 1950, Moyer and Womack 1950, Fitzgerald and Keen 1964, WHO Expert Committee 1965, Sisk 1968). However, as seen later, there is no self-evident dividing line between these two groups and with any form of glucose tolerance test so far devised an unbroken range of results is possible in a given population from the obviously normal to the definitely abnormal (Mitchell and Strauss 1964, Sharp et al. 1964). Inevitably, therefore, any criteria will be more or less arbitrary.

In this study it has been necessary to use the oral glucose tolerance test (OGTT) to standardise the normal range for a series of

intravenous glucose tolerance tests (IVGTT). There is little to choose between the various criteria suggested by different authors for a normal OGTT and so the limits set out on p. 88 have been adopted. These are manifestly arbitrary standards and it must not be assumed, therefore, that figures only slightly in excess of those given necessarily imply a diagnosis of diabetes. Furthermore, (whatever the actual blood glucose or blood sugar levels decided upon), in view of the three quite distinct criteria used, (that is, fasting, peak and two-hour blood glucose/blood sugar levels), the interpretation of and definite diagnosis by an OGTT will inevitably remain in doubt in a large number of cases. One incidental purpose of the present study, therefore, is to show that the IVGTT is more satisfactory both for diagnosis and for definition.

Grades of diabetes

There remains the question of classifying the severity of the disease in diabetic subjects. Early investigators in this field graded diabetics according to the maximum amount of carbohydrate tolerated before glycosuria resulted. This was abandoned when it was realised that results were materially influenced by the protein and fat content of the diet. Subsequently diabetics were variously subdivided into mild, moderate or severe according to their insulin requirements, degree of glycosuria, maximum blood sugar or time taken by the blood sugar to regain fasting levels following a standard glucose load, (Wishnofsky 1928, Joslin 1959b) or by assaying serum insulin levels, (Bornstein and Lawrence 1951). All these methods also broke down

because of the influence of diet and other factors in treatment. In fact, Joslin (1959b) has stated that " a diabetic may be mild, moderate or severe, largely as the doctor with his diet, insulin and exercise, makes him." At the present time a common clinical differentiation is as follows:-

(a) Mild diabetes - Adequate control (that is, blood sugar not exceeding 200-220 mg per 100 ml at any time of the day) with diet alone or diet and oral antidiabetic drugs.

(b) Moderately severe diabetes - Adequate control possible only with the aid of insulin but not liable to ketosis.

(c) Severe diabetes - As for "b" but with a liability to ketosis.

In many ways these distinctions are no less arbitrary than the definition of diabetes itself. They are, however, practicable and of useful therapeutic application. As such, therefore, they are retained for use in subsequent sections of this study.

DISTRIBUTION AND FREQUENCY

Historical and general

Over the years changing estimates of the incidence of diabetes reflect alterations in current views regarding its nature and definition. They also closely parallel developments in the techniques of diagnosis. In 1875 Bouchardat said that "among 20 men between the ages of 40 and 60 years belonging to legislative assemblies, in noted learned societies, occupying high positions in commerce and finance and even in the army, one is sure to find a glycosuric", (quoted by Joslin and Krall 1959). In spite of this prediction, since shown to be substantially correct as far as Western Europe and North America is concerned, diabetes itself was relatively infrequently recognised up to about 1900. Even then diagnosis was usually only made when the disorder presented in severe form. This period may be termed the clinical phase of diabetes and at that time the gross incidence of the disease was put at about 0.1% (Sharp et al. 1964).

The next fifty years was the "biochemical" phase when a variety of different diagnostic techniques were introduced. Rather surprisingly (for the investigators at that time) marked impairment of glucose tolerance was found in many individuals without florid signs or symptoms of diabetes. During this period diabetes was assessed on the basis of mortality rates (De Porte 1929, Marks 1946,) or insurance statistics (Barringer 1909), and several studies were made in such groups as army

recruits (Blotner 1946), factory workers (Gates 1942), volunteers in house to house diabetic "drives" (Beardwood 1944, Sharkey et al. 1950) or consecutive hospital in-patients (Scott and Griffith 1957, Cosnett 1959). Each of these groups was, of course, specially selected in some way and therefore gave a false impression of diabetic incidence. However, on the basis of this work the frequency of diabetes was re-assessed variously at between 0.35% (Marks 1946) and 1.85% (Barringer 1909).

The first full scale whole population survey was in 1946 at Oxford, Massachusetts (Wilkerson and Krall 1947). 70.6% of the total population of 4983 were screened for glycosuria and raised 1-2 hour post prandial blood sugar levels. In addition to 40 individuals already known to have diabetes, 30 new diabetics were discovered - a total incidence of 1.4%. This was the beginning of the "population survey" phase in diabetic diagnosis. Many similar studies have since been undertaken - over a hundred such in the U.S.A. and Canada alone (Krall 1959). Table I lists the principal details from ten of the better documented surveys carried out in Britain and North America. It will be seen that with this type of screening technique the frequency of diabetes seems fairly uniform at about 1.2% - 1.4%.

This estimate does not necessarily apply to other areas. Even by the beginning of the present century great variation had been noted among different religious classes in India (Charles 1907) and more recently population surveys similar to those above have been carried out in a number of different racial groups in other countries (Mills 1930,

Authors	Date	Place	Population	% tested	Glycosurics No.	Glycosurics %	Abnormal GTT No.	Abnormal GTT %	Diabetics Known No.	Diabetics Known %	Diabetics New No.	Diabetics New %	Diabetics Total %
Wilkerson and Krall	1947	Oxford, Massachusetts	4,983	70.6	183	5.21	78	1.56	40	0.80	30	0.60	1.40
Kenny et al.	1951	Ontario	3,502[1]	81	92	2.62	63	1.80	28	0.75	16	0.50	1.25
Kenny and Chute	1953	Ontario	10,186[1]	54	96	1.44	95	1.40	52	0.75	35	0.50	1.27
Redhead	1960	Newcastle on Tyne	9,940	20[2]	105	5.27	62	3.11	9	0.45	19	0.95	1.40
College of G.P.'s Working Party	1962	Birmingham	19,412	95.5	612	3.30	416	2.25	119	0.64	127	0.69	1.33
Harkness	1962	Halstead, Essex	6,132	95.3	186	3.03	-	-	38	0.62	35	0.57	1.14
Stewart and Robertson	1963	Forfar, Angus	10,758	85.4	302	3.60	161	1.75	54	0.59	34	0.37	0.96
Mitchell and Strauss	1964	Arbroath, Angus	17,000[1]	66.7	436	3.85	218	1.94	135[3]	1.20[3]	-	-	1.20
Sharp et al.	1964	Bedford	65,000[4]	66	1046	4.10	261[5]	1.02	-	-	261[5]	1.02	-[6]
Walker and Brown	1964	Ibstock,	5,406[1]	81	200	4.84	99	2.40	33	0.80	25	0.60	1.40

Table I. Details of ten diabetic detection surveys.

Notes : * Figures are for % of those tested,

1 Persons over 5 years of age,

2 Constructed random sample,

3 Total known and new diabetics,

4 Persons over 21 years of age,

5 Abnormal test = 2 hour blood sugar (after 50 grams of glucose) > 120 mg/100 ml,

6 Known diabetics excluded, therefore total not given.

Cohen 1954, Cosnett 1959, Krall 1959, Rudwick and Anderson 1962, Campbell 1963, Davidson 1963, Gelfland and Forbes 1963, Sloan 1963, Poon-King et al. 1968). From these surveys the incidence of diabetes has been shown to vary widely from as little as 0.03% in Eskimos (Scott and Griffith 1957) up to 4.9% in pure Hawaian stock (Sloan 1963) and efforts have been made to relate the different incidence to such things as climate (Mills 1930) or dietary habits (Himsworth 1935b).

Asymptomatic diabetes

The above figures include not only those individuals with obvious symptoms and signs of diabetes, (not all of whom, however, will have reported them), but many others with none. As the diagnosis in the latter group usually rests entirely on the results of a glucose tolerance test (GTT) such persons are often referred to as "GTT diabetics". They form a substantial proportion of the total number.

The harder that diabetes is looked for the more commonly it will be found - chiefly by increasing the proportion of GTT diabetics. Thus it has been shown that a glucose oxidase urine testing strip ("clinistix") for detecting glycosuria will reveal twice as many positive reactors as would be found by "clinitest" tablets (Redhead 1960, The College of General Practitioners' Working Party 1963). It is also clear that fifty grams of glucose by mouth is a severer test of the efficiency of carbohydrate metabolism than an ordinary large meal (Kenny and Chute 1953, The College of General Practitioners' Working Party 1962, Keen 1962, Mitchell and Strauss 1964, Sharp et al. 1964) and will reveal a

correspondingly greater number of GTT diabetics.

The College of General Practitioners' Working Party (1962) performed standard fifty gram OGTT's on a random sample of a large population who had not shown glycosuria following the largest meal of the day. They found that as many as 15% now had glycosuria and many also had abnormal OGTT's. Combining these results with those obtained by the initial screening these workers arrived at an estimate of 6.2% for the total incidence of diabetic abnormality in the general population. Using rather less strict criteria, Mitchell and Strauss (1964) found diabetic abnormalities of the glucose tolerance test in as many as 12% of the general population and Sharp et al. (1964) also gave an estimate of 12 - 14% on the basis of a similar survey.

Even this has not contented some workers who feel like Best (1934) that standard OGTT's put too little strain on carbohydrate metabolism. Techniques such as the one-hour, two-dose test (Exton and Rose 1934) and the corticotrophin or cortisone GTT (Berger 1952, Fajans and Conn 1954), have therefore been designed to increase the strain and discover still more diabetics. These procedures will be discussed in a later section.

Diabetic suspects

Any screening test will, of course, reveal not only those individuals with clear cut diabetes but many others with lesser abnormalities of carbohydrate metabolism such as "lag storage" (high peak blood sugar in an OGTT with normal fasting and two hour values),

normal fasting and one hour but slightly higher than normal two hour blood sugar levels and a number of other minor variants. "Renal glycosuria" (glycosuria occuring even at normal blood sugar levels and after an overnight fast) is also sometimes included in this category. Members of this intermediate or indeterminate group are often referred to as diabetic "suspects". They are of great interest and are the subject of several long term follow up surveys (Marble et al. 1939, Wilkerson et al. 1959, Sharp et al. 1964, Walker and Brown 1964).

Even among those individuals classed as normal, however, refined diagnostic procedures indicate that there are grades of normality. Thus, glucose tolerance is significantly worse in persons with a family history of diabetes, but no evidence of diabetes themselves, than in those with no such family history and is worse in close relatives (e.g. identical twins) of diabetics than in those more distantly related (e.g. uncles or aunts), (Taton et al. 1964).

Or again, glucose tolerance may be appreciably poorer (though still within acceptably normal limits) in obese persons than in thin persons (Vajda et al. 1964) and, depending not so much on the degree as on the duration of the obesity, glucose tolerance may show a gradual diminution from normal through the suspect range to frank abnormality (Allison 1927, Ogilvie 1935).

Diabetogenic factors

Obesity is, of course, by no means the only condition associated with an increased incidence of diabetic aberrations, that is, diabetic-like abnormalities of glucose tolerance. Table II lists some of the other conditions associated with reduced glucose tolerance.

This catalogue certainly does not exhaust the possibilities. Indeed, old age itself is frequently associated with reduction in glucose tolerance, as noted originally by Spence (1921) and since confirmed by many other workers (Hale-White and Payne 1926, Allibone and Tunbridge 1939, Joslin 1940, Hoffstetter et al. 1945, Horvath et al. 1947, Wilkerson and Krall 1947, Redhead 1960, The College of General Practitioners' Working Party 1963). The incidence of reduced glucose tolerance appears to increase steadily with increasing age (Keen 1962, The College of General Practitioners' Working Party 1963), and is not merely a result of inactivity, decreased carbohydrate intake or poor intestinal absorption (Smith and Shock 1949, Schneeberg and Finestone 1952). The College of General Practitioners' Working Party (1963) found the incidence of florid or GTT diabetes was 14.5% in those over 50 years of age and Sharp et al. (1964) found that glucose tolerance was at least slightly abnormal in nearly 50% of persons over the age of 70 years - though even on direct questioning only about 3% in fact admitted to any symptoms referable to their deranged carbohydrate metabolism.

If, therefore, diabetic abnormalities occur so frequently and in

Condition	Reference
Thyroid overactivity	Hamman and Hirschman 1917, John 1932, Althausen 1940, Crawford 1940, Root and Bradley 1959.
Thyroid underactivity	Crawford 1940, Scow and Cornfield 1954.
Pituitary overactivity	Hamman and Hirschman 1917, Houssay 1937, Root and Bradley 1959, Young 1961, Luft 1965.
Adrenal overactivity	Hamman and Hirschman 1917, Houssay 1937, Sprague et al. 1943, Simpson 1953, Root and Bradley 1959.
Phaeochromocytoma	Freedman et al. 1958, Root and Bradley 1959.
Gout	Weiss et al. 1957.
Alcoholism	Bowman et al. 1939.
Uraemia	Perkoff et al. 1958.
Metabolic acidosis	Mackler et al. 1952, Amatuzio et al. 1953.
Poor nutritional states	Hofmeister 1889, Goldblatt 1925, Blotner 1934, Conn 1940.
Poor antecedent diet (especially if low in carbohydrate)	Bernard 1877, Southwood 1923, Sweeney 1927, Tolstoi 1929, Dann and Chambers 1930, Himsworth 1934a and b, 1935a and b, Chambers 1938, McCullagh and Johnston 1938, Allibone and Tunbridge 1939, Conn 1940, Wayburn and Grey 1942, Silverstone et al. 1957.
Fever or Infection	Hamman and Hirschman 1917, Sweeney and Lackey 1928, Ross and Tonks 1938, Tunbridge and Allibone 1940, Freeman et al. 1944, Paul and Presley 1958.
Liver disease	Himsworth 1933, Ross and Tonks 1938, Soskin 1944, Amatuzio et al. 1953, Megyesi et al. 1967.
Inactivity or Bed rest	Loeb and Stadler 1914, Blotner 1945.

Table II. Conditions associated with reduced glucose tolerance.

Condition	Reference
Disseminated sclerosis	Henneman et al. 1954b.
Psychosis	Lawrence and Buckley 1927, Henneman et al. 1954a.
Fear or Excitement	Charles 1907, Folin et al. 1914, Hale-White and Payne 1926, Ross and Tonks 1938, Hinkle et al. 1950.
Drugs - Corticosteroids	Sprague et al. 1943, Ingle 1950, Fajans and Conn 1954 and 1961, Volk et al. 1955, Conn 1958, Dunlop et al. 1959a.
- Sedatives or Hypnotics	Macleod and Pierce 1915, Ross and Tonks 1938, Hunter and Greenberg 1954, Merrivale and Hunter 1954.
- Benzothiadiazine diuretics	Lancet 1965, Breckenridge et al. 1967.
Myocardial infarction	Vallance-Owen and Ashton 1963.
Poor blood supply to large muscle masses	Cajori et al. 1925, Loughlin et al. 1943.
Trauma	Howard 1955, Ross et al. 1966.
Paget's disease	Moehlig and Abbott 1947.
Neoplasia	Rohdenberg et al. 1919, Lozner et al. 1941, Marks and Bishop 1957.
Pregnancy	Lund and Weese 1953, Jackson 1955 and 1959, Hagen 1961, O'Sullivan 1961.
Especially with :	
(a) increasing parity	Lund and Weese 1953, Wilkerson et al. 1959, Fitzgerald et al. 1961.
(b) big babies or foetal abnormalities	Wilkerson et al. 1959, Fitzgerald et al. 1961.

Table II (continued). Conditions associated with reduced glucose tolerance.

so many conditions we are in some difficulty regarding our definition and there is considerable justification for Keen's (1962) remark that, "We are all diabetics, some of us more than others." Does a definition which includes so many individuals within its scope mean anything? Should all those so included be treated alike as suffering from a serious or potentially serious disease? Is any useful purpose achieved by making the diagnosis at all in the majority of cases? Perhaps we should abandon the term "diabetes" altogether now and refer simply to benign and malignant hyperglycaemia (Butterfield 1962)?

The main purpose of a definition is to provide an adequate basis for diagnosis and therapy. While, therefore, in the case of diabetes it must clearly be recognised that all definitions at the present time are arbitrary and provisional, the criteria suggested in the first section (pp 7,8; See also p. 88) have at least the merit of convenient diagnostic applicability. By itself, of course, this is not enough and it remains to be seen whether they also form a satisfactory guide to therapy. For this reason, therefore, before passing to the description and discussion of the main diagnostic tests for diabetes it is necessary briefly to examine two further questions.

DIABETIC SUSPECTS

I. How suspicious should one be of the so-called diabetic "suspects"? What proportion of them do, in fact, develop clinical diabetes?

Definitions

The term "diabetic suspect" is used to describe at least three different groups of individuals. A World Health Organisation Expert Committee (1965) has proposed names and definitions for two of these groups as follows:-

Potential diabetics

1. The identical twin of a diabetic;
2. A person with both parents diabetic;
3. A person with one diabetic parent whose other non-diabetic parent has or had a diabetic parent, sibling or offspring or a sibling with a diabetic child;
4. A woman who has given birth to a live or stillborn child weighing 4.5 kg or more at birth or to a stillborn child showing hyperplasia of the pancreatic islets not due to rhesus incompatibility.

Latent diabetics

1. A person in whom the GTT has produced a normal result but who is known to have been diabetic according to the GTT at some time during pregnancy, during infection, when under some other stress or when obese.
2. A person who has abnormal blood-glucose

responses (similar to those found in diabetes mellitus) to provocative tests, such as the cortisone-augmented GTT.

The third group of suspects may be said to manifest "spontaneous" diabetic aberrations. That is, they are found on testing to have unexplained glycosuria or other minor abnormalities of glucose tolerance not marked enough to bring them within the arbitrary definition of diabetes proper. They are otherwise in good health and do not belong to either of the first two groups.

POTENTIAL DIABETICS

With the recognition of diabetes as at least partly genetically determined (Pincus and White 1933, Ponteva 1938, Blotner 1946, Steinberg 1959, White 1959a, Nilsson 1962, Taton et al. 1964, The College of General Practitioners' Working Party 1965), interest has centred increasingly on those persons with a strong family history of the disease in whom, evidently, there is a greatly increased risk of diabetes. Thus, Joslin et al. (1937) found that out of 13 pairs of identical twins, one each of whom had diabetes, the second twin also had diabetes in nine cases, compared with only two such examples in the non-identical twins of 16 other diabetics.

Berg (1939) traced the identical twins of 46 established diabetics and found that 30 of them also had diabetes, compared with 18 diabetic non-identical twins of 80 further diabetics.

White (1959a) also reports comparable figures of 16 diabetic "pairs" out of 33 sets of identical twins, one each of whom had diabetes, as against two diabetic "pairs" in 63 sets of non-identical twins.

As the relationship to a diabetic becomes more distant the chance of developing diabetes becomes less, although still higher than a comparable group of normal controls (Joslin et al. 1937, White 1959a, Wilkerson et al. 1959, Pfeiffer and Ziegler 1965, Cooke et al. 1966, Hunter and McKay 1967) and this close correlation between nearness of relationship to a diabetic and reduction in glucose tolerance may be seen even among those individuals within the range of normal (assessed by a standard GTT), (Taton et al. 1964, Pyke and Taylor 1967, Taylor et al. 1967).

In women of child bearing age there is an increased tendency to foetal abnormality, perinatal mortality or other obstetric accidents in individuals who subsequently develop diabetes or who are at the time of pregnancy diabetic suspects for any reason (Miller et al. 1944, Miller 1946, Barns and Morgans 1948, Paton 1948, Patterson and Burnstein 1949, Moss and Mulholland 1951, Cosnett 1959, White 1959c, Jackson 1960) although some have denied this (Dolger and Herzstein 1944).

LATENT DIABETICS

1. Stress situations

Many of the stresses referred to in this group are relatively short lived - for example, subarachnoid haemorrage, myocardial infarction,

burns or acute infections - and diabetic aberrations are similarly transient although occasionally a permanent diabetic state may first become apparent at such a time (Hinkle et al. 1950, Roe 1963, Peters and Hales 1965). No long term studies in these individuals appear to have been undertaken and there is therefore no evidence as yet that these patients are more likely to develop clinical diabetes than the general population. Where, however, the stimulus for the diabetic aberration is such that it can act for prolonged periods or repeatedly there is good evidence that diabetes can and often does result. Such a sequence is seen in acromegaly (Hamman and Hirschman 1917, Houssay 1937, Root and Bradley 1959, Young 1961, Luft 1965), pregnancy (Joslin et al. 1936, Lund and Weese 1953, Pyke 1956, Cosnett 1959, Wilkerson et al. 1959, O'Sullivan 1961, Wildberger and Ricketts 1963), hyperadrenocorticism (Hamman and Hirschman 1917, Sprague et al. 1943, Simpson 1953, Root and Bradley 1959) and obesity (Joslin et al. 1935, Ogilvie 1935, Cosnett 1959, Wilkerson et al. 1959). Himsworth (1935b) Vallance-Owen and Lilley (1961) and O'Sullivan and Mahan (1965) have, however, suggested that obesity is a result rather than a cause of diabetes. Likewise, Jackson and Woolf (1957) and Jackson (1959, 1960) while agreeing that glucose tolerance is reduced during at least the first trimester of pregnancy deny that permanent diabetes is produced as a result. Hyperthyroidism is also said to precipitate the onset of diabetes (Shpiner 1930, John 1932, Dunlop et al. 1959c, Root and Bradley 1959) but others (Althausen 1940, Simpson 1956) doubt if a true diabetic state exists more commonly in thyrotoxic than in

euthyroid subjects.

Undoubtedly, some of this group of suspects will develop florid diabetes. In practice, however, such patients present comparatively little problem, in that there is usually an obvious cause for their biochemical disturbance. If this cause is recognised and corrected early enough the onset of clinical diabetes may be considerably delayed or even prevented altogether.

2. "Provocative" glucose tolerance tests

Studies have been made in diabetic suspects by means of "provocative" GTT's such as the ACTH or cortisone GTT (Berger 1952, Fajans and Conn 1954, Duncan 1956b). These studies have usually been in women suspect on account of pregnancy glycosuria, a history of obstetric accidents or large babies (Jackson and Woolf 1957) or individuals with a strong family history of diabetes (Fajans and Conn 1954, Duncan 1956b, Nilsson 1962, Medley 1965). Although some workers have not found these tests satisfactory (Jackson 1960, West 1960, Nilsson 1962), others report a much higher incidence of abnormal results in diabetic suspects than in matched controls (Berger 1952, Duncan 1956b, Fajans and Conn 1959, Goto et al. 1960). These findings were interpreted as showing that frank diabetes is "nearer the surface" in such individuals and more likely to manifest itself spontaneously or following some naturally occuring stress than in normal people. Follow up studies, however, have not so far been long enough to prove this point.

SPONTANEOUSLY OCCURRING DIABETIC ABERRATIONS

With regard to the prognosis in the third group of suspects opinion is even more divided. Lawrence (1928) stated that renal glycosuria is "entirely different from true diabetes ... it ... is not progressive and requires no treatment," and this is echoed by Marble (1959b). Smelo's (1956) view is that there is no evidence that minor abnormalities in the glucose tolerance curve ever deteriorate to become frankly diabetic and similar doubts have been expressed by others (The College of General Practitioners' Working Party 1962).

Survey follow up

Nevertheless while diabetes may develop only rarely in true renal glycosuria there is a mounting body of evidence that such a progression does, in fact, take place fairly frequently in other forms of non-diabetic glycosuria. On general grounds it would seem likely that reduced glucose tolerance occurring spontaneously is more suspicious than that which follows some obvious precipitating event. Marble et al. (1939) followed (for up to 35 years) 1946 patients presenting with glycosuria in whom diabetes had originally been excluded. They found that 193 (9.9%) subsequently developed the disease and all except one of these (a case of pregnancy glycosuria) had had minor abnormalities of the GTT in addition to glycosuria when first seen. They found that the higher the blood sugar levels were initially the greater was the risk of subsequent diabetes.

Wilkerson and Krall (1947) in their large scale survey followed the progress of three broad groups classified respectively as normal, suspect and diabetic on the basis of standard OGTT's. After 16 years they found that of 84 original suspects still living in the area, 24 had become florid diabetics compared with 171 originally normal persons, of whom only 5 had become diabetic. These authors also found that the higher the blood sugar in the original OGTT the more likely the suspect was to develop diabetes. No mention is made by these authors of any suspects who reverted to normal during the same time. Out of 17 "unclassified" glycosurics (that is, those with glycosuria but without an abnormal OGTT), 4 developed diabetes after 4 years (Wilkerson et al. 1962).

McCullagh et al. (1954) made a retrospective study of 200 out-patients who had not been diagnosed as diabetic at the time of their initial visit but who had had elevated blood sugar levels without glycosuria. They estimated that these patients were twice as likely to develop diabetes as individuals with normal initial blood sugar levels. Ackerman et al. (1958) also examined 31 individuals three months to twenty-two years after an initial diagnosis of non-diabetic glycosuria. They found 4 with florid diabetes and 17 others with GTT diabetes.

Walker and Brown (1964) in a five-year follow up of their population survey found that of 32 suspects still available, 7 (22%) had become frankly diabetic, 10 remained suspect, 8 had persistent glycosuria but now had a normal result to an OGTT and 7 were quite normal. This compared with 21 individuals (0.7%) out of the original

control group of 2957 who also developed diabetes during the same interval. Of 61 persons who showed glycosuria but had a normal OGTT originally, one developed diabetes and 10 more were now graded suspects.

OTHER BIOCHEMICAL ABERRATIONS

Finally, an important recent advance in the investigation of this problem is the discovery of the occurrence of certain phenomena associated with the diabetic state in many diabetic suspects from any of the above three groups. These phenomena are manifold and include the following:-

Raised fasting levels of non-esterified fatty acids (Hales et al. 1965, Pfeiffer and Ziegler 1965).

Increased insulin-like activity (Jackson and Keller 1962, Camerini-Davalos et al. 1963, Pfeiffer and Ziegler 1965).

Increased immunologically measurable insulin (Hales et al. 1965, Pfeiffer and Ziegler 1965).

A sluggish rise of insulin-like activity in the serum following a glucose load (Grodsky et al. 1965, Pfeiffer and Ziegler 1965).

An increased fraction of not fully active bound insulin, both before and after glucose, with a normal rise in the free insulin fraction (Camerini-Davalos et al. 1963, Pfeiffer and Ziegler 1965).

A lower than normal fall in blood sugar following intravenous tolbutamide (Jackson and Keller 1962).

Raised serum levels of human growth hormone, with resistance to the diabetogenic effects of exogenous human growth hormone (Pfeiffer and

Ziegler 1965).

Increased insulin antagonism by certain serum albumen fractions or other serum factors (Vallance-Owen and Lilley 1961, Stimmler and Elliott 1964).

Increased urinary albumen excretion (Keen and Chlouverakis 1964).

Early microangiopathy in the capillaries of the ear lobe and renal glomeruli (Camerini-Davalos et al. 1963. Pfeiffer and Ziegler 1965).

Studies in juvenile pre-diabetics during the years just before the onset of the disease (that is, when they were still diabetic suspects, usually for genetic reasons) have shown that they have an increased adolescent growth spurt, bone development and sexual maturity, raised levels of serum follicle-stimulating hormone and urinary 17-ketosteroids, not infrequent hypoglycaemia and a diabetic vascular pattern in the bulbar conjunctivae (White 1959b).

None of the phenomena referred to are absolutely specific for diabetes - indeed, if they were the individuals displaying them would no longer be merely "suspect", they would be diabetic. The microangiopathy seen in these cases is said to be still within the range of physiological variation (Camerini-Davalos et al. 1963) and has been described in normal controls (Moore and Frew 1965). Similar alterations in non-esterified fatty acid levels to those mentioned above may also be seen in thyrotoxic patients (Hales and Hyams 1964) or even normal subjects (Hales et al. 1965). Nevertheless, the evidence provided by these observations strongly supports the belief that diabetic suspects -

of whatever group - have a much greater likelihood of developing florid diabetes than do a comparable group of normal subjects.

II. What is the purpose of early and accurate diagnosis in subjects with a diabetic tendency? Is any real benefit conferred by the discovery and treatment of the large number of mild and GTT diabetics or diabetic suspects now known to exist?

This question may be approached from three aspects.

SYMPTOMS

Rapid correction of the biochemical disturbance in a severe diabetic brings about such obvious improvement that supporting references are unnecessary. Much less widely appreciated, however, is the fact that many individuals found during routine investigation to have diabetes - often only in mild form - have symptoms, sometimes of long standing and hitherto unrecognised both by themselves and their medical attendants (Andrews 1957, Ellenberg 1958, The College of General Practitioners' Working Party 1962, Mitchell and Strauss 1964). Kenny et al. (1951) reported that as many as 17 of the 21 diabetics discovered in their survey had at least one symptom of diabetes and Reid (1960) states that 48% of the newly discovered diabetics in his series had had symptoms for more than four months and 20% for more than a year. Mild though these symptoms often are, they are alleviated by appropriate treatment and patients feel better for it. In addition, of course,

control can now be adequately supervised, minor ailments such as obesity, pruritus or paraesthesia may be attended to, the risks of dangerous ketosis or (in women of childbearing age) obstetric accidents are substantially reduced and, probably, the expectation of life is increased.

BIOCHEMISTRY

1. Diet

The effect of diet on glucose tolerance has been known since at least the time of Claude Bernard (1877) who noted that after a severe reduction in the proportion of dietary carbohydrate glycosuria might occur following a glucose load. This observation has been amply verified by other workers (Southwood 1923, Sweeney 1927, Tolstoi 1929, Dann and Chambers 1930, Himsworth 1935a, Conn 1940).

Hamman and Hirschman (1919) observed the complementary effect, that is, that glucose loads repeated at short intervals gave progressively less hyperglycaemia. Himsworth (1933, 1934a and b, 1935 a) confirmed these findings, not only in respect of repeated doses of glucose but with regard to the carbohydrate content of the diet as a whole. Ellis (1934) applied these observations clinically and reported dramatic improvement in eight severe diabetics (judged by insulin requirements, blood sugar levels and ketosis) with repeated large doses of glucose and insulin. Himsworth (1935b) extended his earlier assertion by suggesting that the development of diabetes itself depended largely on the nature of the antecedent diet. He maintained that, provided the total calorie intake was not too large, persons eating

proportionally more carbohydrate were less likely to develop diabetes than those taking diets relatively rich in fat. Figures for the dietary habits and mortality rates from diabetes among various racial groups were published to support this argument. Although not abandoning this idea himself, (Himsworth 1949), it does not seem to have been followed up by others. Some, indeed, have categorically denied that the proportion of dietary carbohydrate and fat has any bearing at all on the development of diabetes (Joslin et al. 1934, Poulsen 1941). The trend has rather been in the opposite direction and correction of obesity, especially by reduction in the carbohydrate component of the diet, has been shown to be followed by improved glucose tolerance and reduced glycosuria, blood sugar levels, insulin requirements and diabetic mortality (Allen 1914, Newburgh and Conn 1939, Himsworth 1949, Fraser 1965). Karam et al. (1965) and Rudnick and Taylor (1965) also showed an improvement in the serum insulin response to glucose loads after reduction to normal weights of diabetic and non-diabetic individuals.

Similar benefits have been shown to result from strict dieting even without weight loss. Watson (1942) gave 45 subjects with minimal to severe reduction of glucose tolerance a low calorie, fat restricted diet. After up to nine years on this regime and in many cases without significant alteration in weight, the majority had normal or near normal glucose tolerance.

2. Drugs

Haist et al. (1940) showed (in cats) that injected insulin protected the pancreatic islet cells from exhaustion and ultimate degeneration produced by excess pituitary growth hormone. These findings were confirmed by Lukens and Dohan (1940) who concluded that insulin may prevent, restore or hinder the development of islet cell degeneration and functional (that is, overt) diabetes. Fajans and Conn (1960) and Phear (1962) showed that in younger patients with mild or asymptomatic diabetes, glucose tolerance is improved by administration of sulphonylurea drugs and Grodsky et al. (1963) reported that in non-diabetic overweight subjects insulin secretion in response to glucose was restored to normal by diguanide compounds.

Baker et al. (1955) found that while the α/β lipoprotein ratio was higher than normal in diabetics generally it was more so in diabetics with evidence of atheroma than in those without. Poor diabetic control in younger patients and the presence of obesity in older patients appeared to be the chief factors associated with this altered ratio.

Schrade et al. (1963) also reported that in young, well controlled diabetics serum non-esterified fatty acids and triglyceride levels were raised but cholesterol and phospholipids were normal. In older arteriosclerotic or young, poorly controlled diabetics all four fractions were increased. This compared with arteriosclerotic non-diabetics, in whom similar changes were found, except for normal or

depressed levels of non-esterified fatty acids.

One possible interpretation of these findings is that good control in the younger diabetic may prevent or delay the rise of cholesterol and phospholipid serum fractions which appear to be related to arteriosclerotic vascular lesions.

HISTOPATHOLOGY

On the subjects of the preceding two sections there is a general measure of agreement among workers in this field and controversy centres chiefly around this third element of the diabetic state. The overall increase in the death rate and decrease in the expectation of life for diabetics of all ages compared with the general population has been amply documented (Beardwood 1944, Joslin 1959c, Wilkerson et al. 1962). Whereas ketosis was by far the greatest single factor responsible for this in the pre-insulin era (Warren and Le Compte 1959), mortality and morbidity now occur chiefly as a result of lesions of the cardio-vascular system, especially in relation to the coronary, renal, retinal or peripheral limb vessels and hypertension (Clawson and Bell 1949, Hardin et al. 1956, Bryfogle and Bradley 1957, Cosnett 1959, Warren and Le Compte 1959, Wilkerson et al. 1959), although Panthania and Sachar (1961) reported no increase in mortality from cardiovascular disease in their series of Indian diabetics. The other major complications are various forms of peripheral neuropathy (Collens et al. 1952, Keen 1959, Root 1959, Lawrence and Locke 1961, Skillman et al. 1961) and an

increased incidence of obstetric accidents and perinatal deaths in diabetic pregnancy (Miller et al. 1944, Wilkerson and Remein 1957, Farquhar 1959).

At least one of these features is seen in nearly all diabetics at some stage of their illness and there is increasing evidence that they are not so much "complications" as originally thought but intrinsic parts of the disease process. The discovery of identical vascular (Camerini-Davalos et al. 1963, Keen et al. 1965, Pfeiffer and Ziegler 1965) and neurological (Ellenberg 1958, Skillman et al. 1961) abnormalities in diabetics before or very soon after their biochemical disturbance is first apparent has strengthened this view. As a result several workers have reasoned that because these changes are apparently not the result of long standing biochemical upset, biochemical control does not and cannot play any part in their prevention.

Thus, diabetic control (assessed usually by blood sugar levels, glycosuria and strictness of adherence to a diet) and/or severity of diabetes (assessed by insulin requirements and the presence or absence of ketosis) is said to bear no relation to the incidence of cardiovascular disease generally (Mirsky 1945, Dolger 1947, Downie and Martin 1959, Markman et al. 1959, Schlesinger et al. 1960, Panthania and Sachar 1961), retinopathy (Dolger 1947, Downie and Martin 1959, Schlesinger et al. 1960, Knowles et al. 1965), renal lesions (Goodof 1945, Downie and Martin 1959) or neuropathy (Collens et al. 1952). In the light of these reports doubts have been cast on the wisdom or necessity for

large scale diabetic detection surveys. For example, Ashton (1963) has stated that the only treatable lethal complication of diabetes is ketosis and it is unnecessary to mount a detection drive to discover this. Also, in view of the greatly increased incidence of reduced glucose tolerance in the elderly, Sharp et al. (1964) hint that perhaps diabetes is just one more manifestation of the normal ageing process and wonder if the young diabetic is merely "one older than his years with respect to his blood sugar." Even the College of General Practitioners' Working Party (1962) seems to look upon early diagnosis in the course of a survey as mainly of research interest, fraught with grave risk to the psyche of the newly discovered "suspect".

Against this nihilistic attitude may be set the views of Joslin and his co-workers at the Joslin clinic (Wilkerson and Krall 1947, Joslin 1959c) as well as others from the British Isles (Lawrence 1951, Scott 1951, Dunlop et al. 1959b). In 1944 Beardwood noted that the overall mortality rate was lower in diabetics who were well controlled than in those with poor control. More detailed studies have since been made with respect to cardiovascular disease generally (Jackson et al. 1950, Keiding et al. 1952, Dunlop 1954), retinopathy (Jackson et al. 1950, Spoont et al. 1951, Keiding et al. 1952, Hardin et al. 1956, Paul and Presley 1958, Markman et al. 1959) hypertension (Jackson et al. 1950, Dunlop 1954, Paul and Presley 1958), nephropathy (Jackson et al. 1950, Wilson et al. 1951a, Keiding et al. 1952, Dunlop 1954, Lambie and McFarlane 1955, Paul and Presley 1958, Johnsson 1960) and neuropathy

(Dunlop 1954, Ellenburg 1958, Markman et al. 1959) to show that there is a significant reduction of these features in well controlled diabetics. Other workers have shown that even though the incidence of these "complications" is more closely related to the duration of the diabetes, yet their severity is greatly influenced by the strictness of control (Wilson et al. 1951b, Johnsson 1960, Collyer and Hazlitt 1961).

These conflicting views are difficult to reconcile. There is increasing evidence that diabetic "complications" and clinical control are not directly related but are both caused by common antecedent metabolic disturbances, probably genetically determined. Thus, both Keen et al. (1965) and Pirart (1965) found a close correlation between blood sugar levels and the incidence of diabetic "complications" in the groups studied. Bloom (1967), on the other hand, found in his series no relation between the average blood sugar in a particular individual and the strictness of his adherence to a treatment regimen. Combining these observations, therefore, it would seem that even the strictest treatment cannot materially influence the development of "complications". It is possible that this view may one day be established as correct but in view of the evidence cited above it must at present still be regarded as unproven. Its corollary - that it is futile to diagnose and treat the asymptomatic diabetic - must also at present be rejected.

As regards the problem of the pregnant diabetic, however, there seems to be no dissent from the general opinion that good control

reduces the incidence of obstetric accidents (mainly toxaemia of pregnancy and hydramnios) and the perinatal death rate (Pederson 1954, Wilkerson and Remein 1957, Carrington and Shuman 1958, Farquhar 1959, White 1959c, Dolger et al. 1962, Jackson et al. 1962). Furthermore this is not only true for established diabetics. Similar beneficial results have followed active treatment even of those women with suspected prediabetes (because of their family or previous obstetric history) or who showed minimal abnormalities of glucose tolerance during early pregnancy (Wilkerson and Remein 1957, Carrington and Shuman 1958, Jackson 1959, Wilkerson 1959).

To summarise, therefore:-

1. The diagnosis of diabetes is important not only for those with florid symptoms and signs but also in the case of diabetic "suspects", many of whom do, in fact, develop frank diabetes later.

2. There is evidence that appropriate treatment does prevent, delay or ameliorate all the major manifestations of the disease and therefore the earlier the diagnosis is made the more likely treatment is to be beneficial.

DIAGNOSTIC TESTS

The Oral Glucose Tolerance Test

HISTORY

Some early approaches to the diagnosis of diabetes have already been mentioned. At first the disease was chiefly recognised on clinical grounds alone (Adams 1856). Hindu writings dating from about the 6th century A.D. tell of the presence of an unnatural sweetness in the urine of diabetics (Bose 1907, Barach 1949) and possibly this fact was known even earlier to Chinese and Japanese physicians (Barach 1949). It was rediscovered in the Western world by Thomas Willis who also noted the sweetness of diabetic urine and claimed that diabetes was a disease primarily producing increased amounts of sugar in the blood which subsequently overflowed into the urine (Willis 1689). Dobson (1776) verified that the blood in diabetes is sweet and demonstrated fermentable sugar in the urine. Finally Chevreul (1815) identified the sugar as grape sugar or glucose.

For some time after Chevreul's discovery diagnosis still depended largely on clinical features but glycosuria was increasingly used as an additional criterion. "Alimentary glycosuria" was the name applied to the glycosuria which followed the oral administration of glucose or other carbohydrate foods and the investigations into this phenomenon provided the forerunners to present day OGTT's. The earliest published account of such experiments appears to be that of Worm Muller (1884) who found little or no glucose in the urine of two

normal men following the ingestion of 50 grams of glucose or 100 grams of lactose. The following year he reported considerable glucosuria after similar carbohydrate loads in three mild diabetics (Worm Muller 1885).

As a result of experimental work with dogs Hofmeister (1889) proposed the term "tolerance" to represent the largest dose of sugar which could be ingested without producing glycosuria. He expressed his results in grams of sugar per kilogram body weight.

Measurement of glycosuria continues to be used to assess the degree of diabetic control but it was soon realised that it was too imprecise by itself to give much information regarding glucose tolerance. There was poor correlation between blood glucose levels and urine glucose concentration (Hopkins 1915, Williams and Humphreys 1919) because of wide variations of renal threshold even in normal subjects (Allen and Wishart 1920, Campbell et al. 1932, Butterfield et al. 1967). Furthermore when glycosuria followed a carbohydrate load its appearance was often delayed until after the time of peak blood sugar levels and disappeared only when the blood sugar had fallen considerably (Hamman and Hirschman 1917, Robinson et al. 1935).

The introduction of Bang's new micromethod for blood glucose determination (Bang 1911, Hopkins 1915) allowed more precise observations to be made on alterations in blood glucose levels following a glucose load and the first reported glucose tolerance test of the type used today was by Jacobsen (1913). He measured the rise

and fall of blood glucose in "normal" subjects (although judging from his case reports several of his patients were far from normal) following the ingestion of various types of food. Numerous other papers quickly followed reporting the blood sugar curve in a variety of diseases. Prominent among these was that by Hamman and Hirschman (1917) who gave fasting subjects 100 grams of glucose in 300 ml of water flavoured with lemon. Samples for blood sugar estimation were taken fasting and at ½, 1, 1½ and 2 hours after the glucose and urine was collected as far as possible simultaneously with the blood.

Blood sugar curves obtained by this technique in normal subjects showed a smooth, moderately rapid rise of blood sugar for the first ½ to 1 hour, from fasting levels of below 120 mg per 100 ml to peak figures of less than 180 mg per 100 ml, followed by an equally smooth fall to fasting levels or just below in 1½ to 2 hours. In the diabetic, on the other hand, not only were the fasting and peak levels usually raised above normal but the time taken to reach the peak and return to the fasting value was prolonged, sometimes considerably.

PHYSIOLOGICAL VARIABLES

There were many factors, however, other than diabetes itself which were capable of producing abnormal glucose tolerance curves and it soon became apparent that repeated tolerance tests often gave inconsistent results. These anomalies might be the result of concomitant disease (see p. 17 and 18) or might even, apparently, occur spontaneously (Gray 1923, Lennox and Bellinger 1927, Soisalo 1929,

Glassberg 1930, Myers and McKean 1935, Freeman et al. 1942, Horvath et al. 1947, Unger 1957).

Gastrointestinal tract absorption. One obvious variable was the rate of glucose absorption from the gastrointestinal tract. Many early workers appear to have assumed not only that glucose absorption was constant for different individuals but also that it proceeded at a uniform rate regardless of the concentration or the total quantity administered (Janney and Isaacson 1918). Cori (1925) gave his subjects glucose in concentrations varying from 25% to 80% and appeared to confirm this view by finding that there was a linear relationship between the amount of glucose absorbed and the time after ingestion. Even when as much as 70% of the original quantity of glucose had been absorbed the absorption rate, he claimed, was unaltered. Warren et al. (1940) also described experiments to show that variations in the concentration of glucose made little difference to the rate of absorption because the rapid dilution of solutions in the stomach soon eliminated initial concentration differences.

Gastric emptying However, by simultaneously measuring gastric emptying, intestinal transit and absorption of test substances, other workers have shown that glucose absorption is influenced by the concentration of glucose and also that increasing the concentration of glucose has a marked effect on the rate of absorption, chiefly by delaying gastric emptying (Mackay and Bergman 1933, Quigley and Phelps

1934, Fenton 1945, Reynell and Spray 1956b).

Fenton (1945) demonstrated that there was little or no glucose absorption from the stomach but his experiments were criticised as being grossly unphysiological by Reynell and Spray (1956a) who showed that glucose absorption did take place in the stomach although the absorptive capacity was soon saturated. These findings were confirmed by Warren et al. (1940) who demonstrated, however, that absorption from the upper small intestine was better. If, however, high concentrations of glucose inhibited gastric emptying, the intestinal load of glucose would not increase proportionally. Therefore the intestinal absorption rate would increase less in proportion to a larger load, although absorption would go on for longer.

The effect of disordered gastric emptying on the glucose tolerance test may also be seen after stomach operations such as partial gastrectomy or gastro-enterostomy where emptying is very rapid (McKean et al. 1935, Myers and McKean 1935, Evenson 1942, Gilbert and Dunlop 1947, Zollinger and Hoerr 1947). In these circumstances blood sugar curves characteristically rise very rapidly to a peak figure often exceeding 200 mg per 100 ml even in non-diabetics and fall again equally rapidly, sometimes to severe hypoglycaemic levels. On the other hand, if the subject is nauseated (perhaps from the strong glucose solution) or excited, gastric emptying may be delayed and the slow absorption will produce flat blood sugar curves (Hale-White and Payne 1926). Nisell (1957) also found that the supine position during

the test or insufflation of intragastric CO_2 or O_2 increased glucose tolerance (that is, produced flatter blood sugar curves), presumably also by delaying gastric emptying. Paradoxically, in pyloric stenosis, where gastric emptying is also slow, prolonged hyperglycaemia in non-diabetics has been observed (Meyers and McKean 1935).

Intestinal mucosa. More important even than variations in gastric emptying time in determining the rate of absorption is the state of the intestinal mucosa. Diminished absorption and flat blood sugar curves in steatorrhoea were first demonstrated by Thaysen and Norgaard (1929). These workers also performed IVGTT's in their patients and found diabetic-like curves, but because of the normal rise in the respiratory quotient during these tests, concluded that the fault lay with the endocrine glands concerned with glucose metabolism rather than with intestinal absorption itself. Other workers, however, have shown that absorption is affected in conditions causing steatorrhoea (Fairley 1936, Groen 1938, Ross and Tonks 1938, Lozner et al. 1941, Frazer et al. 1952, Taylor and Wightman 1952), although the efficiency of absorption is not closely correlated with the clinical state (Taylor and Wightman 1952). Poor glucose absorption may lead to systemic carbohydrate deprivation and diabetic-like blood sugar curves during an IVGTT. Moreover, if the two opposite processes - poor absorption leading to flat GTT curves and carbohydrate deprivation leading to diabetic curves - are nicely adjusted in a particular individual, OGTT's may even give an entirely normal curve (Ross and Tonks 1938).

In steatorrhoea associated with the coeliac syndrome definite histological changes are present in the small intestinal mucosa, but other unrelated disorders may also produce functional mucosal disturbance and absorptive defects. Groen (1938) found reduced absorption in such differing conditions as pernicious anaemia, pellagra, ulcerative colitis and tuberculous enteritis and Althausen (1940) reported diabetic or "lag-storage" blood sugar curves in thyrotoxicosis and flat curves in myxoedema. These were shown to be partly because of disordered gastric and intestinal motility and partly as a result of functional alterations in the intestinal mucosa.

VARIATIONS OF TECHNIQUE

Even if there was agreement on the physiological principles involved, there are numerous differences of opinion regarding the technique, method of calculation and interpretation of these tests.

Diet. The importance of an adequate carbohydrate intake for a few days at least before a GTT has already been pointed out (p.17). It is not entirely clear, however, what constitutes an "adequate" diet. Conn (1940) proposed an intake of at least 300 grams of carbohydrate for five days before a test and this practice is still frequently adopted (Unger 1957). Other workers, on the other hand, have shown that a diet containing as little as 150 grams (Marble 1959a, Wilkerson et al. 1960), 125 grams (Mosenthal and Barry 1950), or even 100 grams (Irving and Wang 1954) of carbohydrate is adequate preparation. Indeed,

Dann and Chambers (1930) report that even after three weeks fast, diabetic-like blood sugar curves in normal subjects could be corrected completely by four further days on a diet containing as little as 50 grams of glucose daily.

As to the remainder of the diet, Jacobsen and Edwards (1920) showed that the proportion of protein and fat made little difference to glucose tolerance, but Du Vigneaud and Karr (1925) and Srinivasen (1957) reported that a good protein intake before a test improved glucose tolerance, while a high proportion of fat decreased it.

Activity. Comesatti (1907), in experimental animals and Devlin (1963), in humans, have both shown improved glucose tolerance after a period of training. Prolonged inactivity is associated with reduced tolerance (Loeb and Stadler 1914, Blotner 1945). During a GTT it is customary to keep the subject at rest.

Pre-test fast. It is usual to perform a GTT after an overnight fast but four hours (Hale-White and Payne 1926) or five hours (McLean and De Wesselow 1921) are probably sufficient in most cases. Fenton (1945) reported delay in gastric emptying and distortion of the blood sugar curve if the pre-test fast was prolonged beyond 48 hours.

Dose of test substance. Myers and McLean (1935) described satisfactory GTT results following a variety of carbohydrate foods, including potatoes, oatmeal and bread, but the usual test substance is dextrose. In the

United States this is commonly given in a dose of 100 grams (Hopkins 1915, Wilkerson and Krall 1947, Marble 1959a), while in the British Isles the dose is more often 50 grams (Hale-White and Payne 1926, Walker 1959, The College of General Practitioners' Working Party 1962, Sharp et al. 1964). Hagedorn (1921) and Hale-White and Payne (1926) claimed that the peak rise observed in a GTT varied directly with the dose of glucose and some workers therefore adjust the dose according to the subject's weight (Janney and Isaacson 1918). Others have shown that there is no need for this unless, perhaps, the subject is grossly over or underweight. Increasing doses of glucose evidently have very little effect on the peak height of GTT curves, although they may delay the return to fasting levels (McLean and De Wesselow 1921, Gray 1923, Rowe and Rogers 1927).

Blood sugar estimation. Results obtained in apparently comparable groups of subjects may vary considerably according to whether the blood is venous or capillary and whether "blood sugar" (i.e. glucose + saccharoids - see p. xiv) or "blood glucose" alone is measured. Mosenthal and Barry (1946) found that differences of up to 70 mg. per 100 ml might exist between "blood sugar" (as defined above) and true glucose. During the preliminary stages of the present study both methods were used and similar differences were also observed. Moreover, such differences were not a constant proportion of the total reducing substances and could not therefore be accurately allowed for.

INTERPRETATION.

Until fairly recently no settled standards of normality existed either for the type of subject studied (see some of the "normal" subjects reported by Jacobsen (1913)) or for blood sugar levels (Gray 1923) and this fact contributed largely to the anomalous, even bizarre conclusions among earlier workers. Of the three salient features of an OGTT curve, viz. fasting blood sugar, peak level and time taken to return to normal fasting levels, the fasting blood sugar has been shown to be quite unreliable as an indication of mild diabetes, although it will commonly be raised in a severe case (Frethem 1963, Mitchell and Strauss 1964, see also the appendix to the present study). As to the remaining two features argument still exists but the time taken to return to the fasting level is normally considered more important (Wishnofsky 1928, Moyer and Womack 1950, Marble 1959a). Standards of normality for blood sugar at various points of the GTT have been agreed upon and have been referred to elsewhere (p.7). (See also p. 88)

This information has been turned to good account by several workers who have tried to simplify the testing of glucose tolerance by estimations of the blood sugar at a single point after a glucose load instead of the usual repeated measurements. Random blood sugar readings were, and still are, used extensively but because they depend on the interval since the last meal they may be misleading. Pedersen and Nissen (1959) suggested averaging several blood sugar readings over three or four days to eliminate the errors inherent in single

random estimations but this seems even more inconvenient than a standard OGTT.

Ralli and Shannon (1931) found good correlation between the clinical severity of diabetes and the 4-hour blood sugar reading during a 5-hour OGTT. Moyer and Womack (1950) compared 2 - 2½ hour post prandial blood sugars with the results of standard OGTT's, 1-hour 2-dose tests (Exton and Rose 1934) and IVGTT's done in the same subjects and found that if a 2-hour post prandial blood sugar of 134 mg per 100 ml was regarded as the upper limit of normal, the single blood sugar reading was effective in detecting the majority of diabetics. Wilkerson and Krall (1947) in their diabetic survey measured the blood sugar 1 - 1½ hours post prandial taking the upper limit of normal as 190 mg per 100 ml (in capillary blood). A single blood sugar reading (in this case, two hours after a main meal) was also used by Stewart and Robertson (1963). They took the upper limit of normal as 130 mg per 100 ml (in venous blood). Mitchell and Strauss (1964) did not agree with this plan, estimating that about 30% of diabetics would be missed if post prandial blood sugar and glycosuria were the only screening procedures used. They recommended a blood glucose reading exactly 2 hours after 50 grams of glucose by mouth as being a more sure method, the upper limit of normal being taken as 115 mg per 100 ml (in venous blood). This procedure was adopted by Sharp et al. (1964) in their very large diabetic detection drive.

Unfortunately notwithstanding all attempts at standardization,

inconsistent results for successive OGTT's in the same individual continue to be reported (Freeman et al. 1942, Horvath et al. 1947, Unger 1957) and constitute a real drawback to the use of the OGTT as an accurate diagnostic technique.

The One-Hour Two-Dose Test

Hamman and Hirschman (1919) showed that the effect of repeated doses of sugar on the blood sugar in normal subjects was different from that found in diabetics. This observation was applied by Exton and Rose (1934) who proposed a new technique as an alternative to the standard OGTT. In this, subjects were prepared in the same way as before and given 50 grams of glucose by mouth, followed by a further 50 grams half an hour later. Blood sugar was estimated fasting and at ½ and 1 hour. Urine samples were taken at the same intervals.

The rise of blood sugar during the first half hour was, of course, the same as for a standard OGTT and was judged by the same criteria. Exton and Rose's full criteria of normality were as follows:-

1. Fasting blood sugar within normal limits (that is, less than 120 mg per 100 ml).
2. A ½ hour rise less than 75 mg per 100 ml.
3. A 1 hour figure of no more than 5 mg per 100 ml in excess of the ½ hour figure.

In their original series of diabetics all had a rise of the 1 hour blood sugar of more than 10 mg per 100 ml over the ½ hour level.

Results falling between these two limits were classified as "suspect".

This test was claimed by its originators to have several advantages over the standard OGTT. There were no discrepancies from the results of OGTT's in obvious cases and there was better differentiation in those with equivocal OGTT results. As it took less time than a standard OGTT it was better for the patient, saving him time, anxiety or boredom. No very concentrated glucose solutions (such as those required by the loading dose of 100 grams of glucose commonly given) were required. Finally it appeared that the necessity for special preparatory dieting was largely eliminated.

These authors were supported in their conclusions by Kelly et al. (1935), Gould et al. (1937), Matthews et al. (1939), Wayburn and Gray (1942) and Goldberg and Luft (1948). Gould et al. (1937) proposed modifications of the criteria. They defined a diabetic result as one showing at least two of the following:-

1. Fasting blood sugar more than 120 mg per 100 ml.
2. A ½ hour blood sugar more than 50 mg per 100 ml over the fasting level.
3. A 1 hour blood sugar more than 30 mg per 100 ml over the ½ hour level.

Matthews et al. (1939) further suggested that the single 1 hour blood sugar reading was as good a criterion alone as the usual three readings. In their series all subjects with a blood sugar at this point of less than 158 mg per 100 ml were normal. All others were classed as "presumptive" diabetics.

This test, however, has not met with general approval. Sweeney et al. (1937) found that the antecedent diet had at least as much effect on the 1-hour 2-dose test as a standard OGTT. Leonards and Free (1945) also largely discredited the test by finding that between 38 and 62 grams of glucose were still in the stomach at the end of one hour and that there was no correlation between the amount of gastric glucose at a given moment and the blood sugar. This would imply that the second dose of 50 grams of glucose had little or no influence on the shape of the curve. Indeed, Warren et al. (1940) had previously shown that the average maximum rate of glucose absorption from the stomach and duodenum combined was in the region of 43 grams per hour. Reports of comparative series have confirmed that the 1-hour 2-dose test is less satisfactory than common alternative tests (Gould 1937, Langner and Dewees 1942, Moyer and Womack 1950) and it is now seldom used.

Cortisone Oral Glucose Tolerance Test

The 1-hour 2-dose OGTT of Exton and Rose (1934) was an attempt to place a greater strain upon carbohydrate metabolism than is usually done with a standard OGTT. The tendency of adrenocortical over-activity or therapeutic adrenocortical hormones to produce decreased glucose tolerance or even frank diabetes has been known for some time (Hamman and Hirschman 1917, Houssay 1937, Sprague et al. 1943, Dunlop et al. 1959a) and Berger (1952) first conceived the idea of producing temporary reduction in tolerance by means of an injection of 100 mg ACTH

one hour before a standard OGTT. In this way he hoped to produce a critical strain and discover those individuals with diminished reserve functional capacity of the pancreatic islet beta cells. In other words, to discover those whose metabolic efficiency with respect to carbohydrates was reduced but appeared normal when faced only with the usual OGTT glucose load. As predicted, he found a definite rise in the general level of the GTT blood sugar curve in some non-diabetic siblings of known diabetics.

In 1954 Fajans and Conn reported similar results in a comparable group by means of oral cortisone instead of ACTH. The same authors have since used the test extensively to study many individuals whom they regard as potential diabetics, usually on genetic grounds.

Goto et al. (1960), comparing the cortisone OGTT with a standard OGTT, calculated indices of difference by taking the sum of the differences in observed blood sugar levels for both tests at the fasting, ½, 1, 1½ and 2 hour points. They found the average "index" for non-diabetic healthy volunteers was 15 compared with 189 in diabetics and 110 in those with a strong family history of diabetes.

Jackson (1960) and West (1960) criticised the test because, they claimed, a number of individuals who were almost certainly pre-diabetics on genetic or obstetric grounds and even some mild diabetics gave a normal response to the test, that is, showed no significant rise of the blood sugar curve following cortisone.

However, Fajans and Conn (1961) continued to report good results.

They found that of 57 individuals who seven years earlier had shown a positive reaction to the test, 15 (26%) were now diabetic and 5 more (9%) had probable diabetes. This compared with 71 subjects who had had a negative test originally of whom only 2 (2.8%) had developed diabetes. This test would appear to have real value in studying the suspected pre-diabetic. A few more years' experience may show more conclusively how reliable it is in predicting the onset of clinical diabetes.

Prolonged Fast

Prolonged carbohydrate deprivation will cause reduced tolerance to sudden glucose loads in both diabetic and non-diabetic subjects (see p.17). Southwood (1963) has suggested that a pre-GTT carbohydrate deprivation of 24 to 36 hours instead of the usual 12 hours may be sufficient to impose a critical strain on an individual's carbohydrate metabolism and produce diabetic abnormalities of the blood glucose curve in a similar way to those produced by the cortisone OGTT. This procedure has the merit of simplicity but it is inconvenient for the subject being tested. Southwood himself only reports one case and no further accounts appear to have been published.

The Intravenous Glucose Tolerance Test

HISTORY

At a very early stage in the development of GTT's investigators explored the possibility of eliminating the errors due to inconsistent gastrointestinal tract absorption by injecting glucose directly into the blood stream. The earliest recorded experiment using this technique (in rabbits) appears to be that of von Becker (1854, quoted by Ross and Tonks 1938) and in fact antedates Worm Muller's first OGTT by 30 years.

Blumenthal (1905) was one of the first to point out that glucose tolerance should be related not merely to the maximum "assimilable" quantity of glucose in a given subject but also to a time factor. He expressed tolerance as the maximum amount of glucose capable of being dealt with in unit time. In rabbits, for example, 0.85 grams of glucose per kilogram body weight per hour was the average maximum which could be given without producing glycosuria but the same quantity could often be given repeatedly at short intervals also without glycosuria.

Woodyatt et al. (1915) - in rabbits, dogs and man - and Allen and Wishart (1920) - in dogs - repeated these experiments and found that glucose tolerance was closely similar in these three species, - approximately 0.8 - 0.9 grams per kilogram body weight per hour.

All these workers used glycosuria as the criterion of tolerance. Thannhauser and Pfizer (1913) were the first to use the IVGTT clinically in human subjects. They gave an infusion of up to 500 ml of 7% glucose over a period of 15 minutes and followed the resultant blood sugar changes.

Allen and Wishart (1920) and Thelheimer et al. (1926) also employed much the same technique, the former, however, using intermittent injections of glucose rather than a continuous infusion. Both sets of authors reported a moderate rise of blood sugar at the start of the infusion followed by a fall about one hour later. This fall often continued to below the starting level even before the infusion had been stopped.

Jorgensen and Plum (1923) introduced the IVGTT as we know it today. Their method was to inject 20 grams of glucose in 50 ml of water over a period of 3 minutes. Blood sugar was estimated fasting, at the end of the injection, every 2-3 minutes for 15 minutes and every 5-10 minutes for up to 2-3 hours. Blood sugar curves obtained in this way in non-diabetic subjects rose rapidly to a peak within 1-2 minutes of the end of the injection (Tunbridge and Allibone 1940, Greville 1943) and fell again to the fasting level or just below over the next 45-60 minutes. In diabetics the peak and the return to normal were delayed but there did not seem to be a close correlation between the peak figures and fasting levels (Jorgensen and Plum 1923).

Although the IVGTT did not win immediate favour it gradually became established and is now increasingly used. It has also remained much the same as regards the actual test procedure. As with the OGTT, however, there has been considerable argument on matters of detail, especially with respect to the interpretation of results.

VARIABLES

Apart from the important factor of gastrointestinal absorption, the same physiological variables exist for the IVGTT as for the OGTT (see p.40).

Similarly, doubt has existed as to the optimum dose and strength of glucose and the rate of infusion. Tunbridge and Allibone (1940) reviewed the literature up to that time and quoted great variation in these details. Different workers have given from 3.5 to 100 grams of glucose in strengths of from 7% to 54% over intervals of from 20 seconds to 30 minutes.

The usual method of administration is by rapid injection of concentrated glucose but slow infusion of weak solutions have occasionally been suggested as being more physiological (Thelheimer et al. 1926, Jokipi and Turpeinen 1954, Hlad et al. 1956).

Just as in the OGTT, many users of the IVGTT vary the dose of glucose in direct proportion to the weight of the individual concerned (McKean et al. 1935, Crawford 1938, Hamilton and Stein 1942). On the other hand, Nilsson (1962) suggests that instead of increasing the glucose load for overweight subjects it should actually be proportionally decreased. In these individuals the volume of extracellular fluid - the volume into which injected glucose rapidly diffuses to become available for metabolism and disposal - is relatively small (Posberg-Petersen 1957). However, Tunbridge and Allibone (1940) and Lozner et al. (1941) found no features in IVGTT results in different individuals

which could be attributed to differences in their weight and in common with Jorgensen and Plum (1923), Ross and Tonks (1938), Amatuzio et al. (1953), Duncan (1956a) and Lundbaek (1962) recommended a constant dose of glucose in all subjects tested. This is usually 25 grams in a strength of 50%.

INTERPRETATION

Criteria for the interpretation of IVGTT results have been subject to much discussion. Jorgensen and Plum (1923) plotted the blood sugar levels obtained in their tests on linear graph paper and expressed their results as the area below the curve plus the time taken for the blood sugar to regain the fasting level.

Other criteria used since that time have been:-

(a) Area below the curve alone (Ross and Tonks 1938),

(b) Time taken for the blood sugar to return to the fasting level (Crawford 1940, Tunbridge and Allibone 1940),

(c) Blood sugar at a certain predetermined time after injection (McKean et al. 1935, Lozner et al. 1941),

(d) Height of peak blood sugar level and time of peak after glucose injection (McKean et al. 1935).

However, several workers have found great variation in peak blood sugar levels in the same individuals with successive IVGTT's when other parts of the curves have not varied and there is no apparent correlation between this feature and the dose of administered

glucose, the fasting blood sugar or the time taken to return to normal (Jorgensen and Plum 1923, McKean et al. 1935, Crawford 1938, Tunbridge and Allibone 1940). Consequently any criterion based on the peak blood sugar figure (all except "b" and "c" above) are fallacious.

Factors in glucose assimilation.

Unfortunately - and this drawback applies equally, of course, to the OGTT - nobody knows precisely what is being measured in a GTT or what exactly is involved in glucose disposal. Clearly several factors play a part. If one plots the blood sugar curve for a normal IVGTT on linear graph paper the curve is seen to drop very steeply at first then gradually becomes less steep until it finally approximates to the original fasting level or drops slightly below. The first rapid fall is partly at least accounted for by rapid dispersal and equilibration of the injected glucose throughout the body's extracellular fluid. A certain proportion may be a result of urinary loss but in a non-diabetic subject this is usually small - between 0 and 2.8 grams following a 25 gram glucose load (Pijoan and Gibson 1938, Tunbridge and Allibone 1940). Then probably follows true cell metabolism of the glucose producing a rather slower fall. Finally, homeostatic mechanisms, especially hepatic glycogenolysis - temporarily inhibited by the sudden rise of blood glucose (Soskin et al. 1938, Searle and Chaikoff 1952) - retard the fall progressively until a fairly steady level is reached and maintained.

Mechanisms concerned with the third phase, especially normal liver

function (Soskin et al. 1934, Lang et al. 1954), undoubtedly play a significant part in the final shape of a blood sugar curve but in the diagnosis of diabetes it is the second phase - true metabolism - with which we are chiefly concerned. Unfortunately the three phases referred to are not mutually exclusive although one or other may be predominant at a given moment, and precise sections of the blood sugar curve cannot be assigned to each one. Assessment of glucose disposal is therefore a crude estimation at best. In fact, gross abnormalities of two opposite metabolic processes may on occasion produce normal or near normal glucose tolerance curves, as was shown by Houssay and Biasotti (1931) with hypophysectomised-pancreatectomised dogs.

Exponential relationship.

In 1930 Fishberg demonstrated that the logarithm of the concentration of certain non-fermentable reducing substances was proportional to the time after their injection into the blood stream. Hamilton and Stein (1942) applied these findings to their study of glucose disposal. They found that although the disappearance of blood sugar in an IVGTT was presumably caused by multiple factors they all seemed to work together (at least between about the 20th and 60th minute after injection of glucose) to produce, in effect, a mono-molecular reaction. In other words the amount of sugar disappearing from the blood during that period was constantly the same percentage of the total quantity present. To put it another way, the rate of

fall of blood sugar at any moment was proportional to the blood sugar at that moment, or $\frac{ds}{dt} = kt$, which on integration gives, $\log S = kt + C$ (where S = blood sugar at any time, t, k and C are constants).

In the present context (for use in actual graphs) this general formula was rewritten as, $\log S = S_o - kt$,

(where S_o = the intercept on the blood sugar scale of the slope extrapolated back to t = 0,

k = a constant representing the slope).

A simple exponential relationship could therefore be demonstrated between observed blood sugar values and time - that is, a straight line resulted if the blood sugar curve was plotted on semilogarithmic graph paper.

Hamilton and Stein (1942) suggested that calculation of "k" would provide a suitable expression of glucose assimilability for a given individual. This "glucose assimilation coefficient" (to use a phrase introduced later by Conard et al. 1953), may be defined as the blood glucose decrease per unit of blood glucose per unit of time. It may be multiplied by a hundred and expressed as a percentage. In practical terms it represents the rate of fall of blood glucose. The larger the value for k, therefore, the faster the fall and the more efficient the body in disposing of glucose. Thus, normal subjects would be expected to have high k values and diabetics low values.

Greville (1943) using all the blood sugar values in an IVGTT between 5 and 90 minutes, claimed that the graph of log blood sugar

against time did not produce a straight line. Instead he related time to the blood sugar value above a theoretical equilibrium level, S_∞ .

S_∞ was calculated as follows:- The curve of blood sugar against time was plotted on linear graph paper (Fig. Ia). The slope of this curve ($-\frac{ds}{dt}$) was then measured for various values of t (time) and a second graph drawn of $-\frac{ds}{dt}$ against blood sugar values Fig Ib).

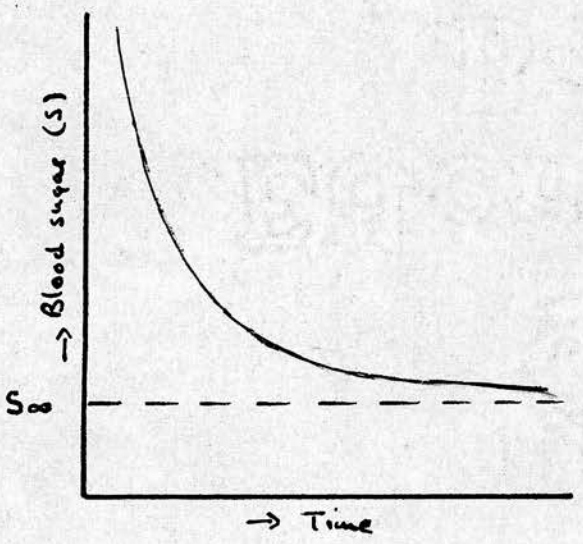

Figure Ia.

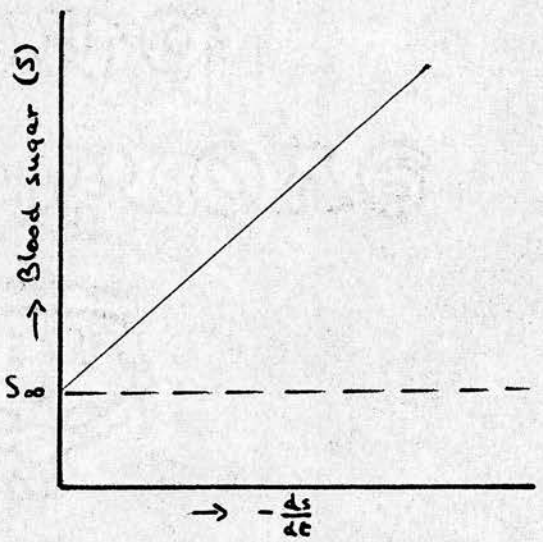

Figure Ib.

Figure Ia. Graph of blood sugar vs. time.

Figure Ib. Graph of blood sugar vs. $-\frac{ds}{dt}$.

The straight line graph of Fig Ib is seen to pass not through zero as might be expected if the fall of blood sugar depended on the total quantity of blood sugar present, but through a certain positive value of S. This represents S_∞ . It may be defined as the blood sugar level to which the falling curve of blood sugar against time (on linear graph paper) appears to approach asymptotically. It was not the initial fasting blood sugar level (usually lying well below it) and was not reproducible in repeated tests; neither was it the physiological equilibrium level, as the blood sugar tended to rise again after passing through this minimum point. Greville himself seems to have regarded it as being of mathematical but not physiological importance. If, then, the fall of blood sugar was proportional to the quantity of blood sugar in excess of S_∞ , the simple exponential relationship described by Hamilton and Stein (1942) had to be amended to give:-

$$\log (S - S_\infty) = \log (S_0 - S_\infty) - kt .$$

Amatuzio et al. (1953) using Greville's formula assumed that for practical purposes S_∞ was equal to the fasting blood sugar and related time to the blood sugar value in excess of the starting or fasting level. These authors used the whole curve from 4 to 72 minutes after the injection of glucose unless the blood sugar fell to within 30 mg per 100 ml of the fasting level.

Continuous infusion.

Jokipi and Turpeinen (1954) returned to the earlier technique of continuous intravenous infusion of glucose, claiming that this provided a more physiological test. They administered 155 to 630 mg glucose over a period of one hour and found that towards the end of this period, in spite of continued glucose infusion, blood sugar levels reached a plateau or even fell somewhat. In other words, at that stage glucose administered equalled glucose eliminated.

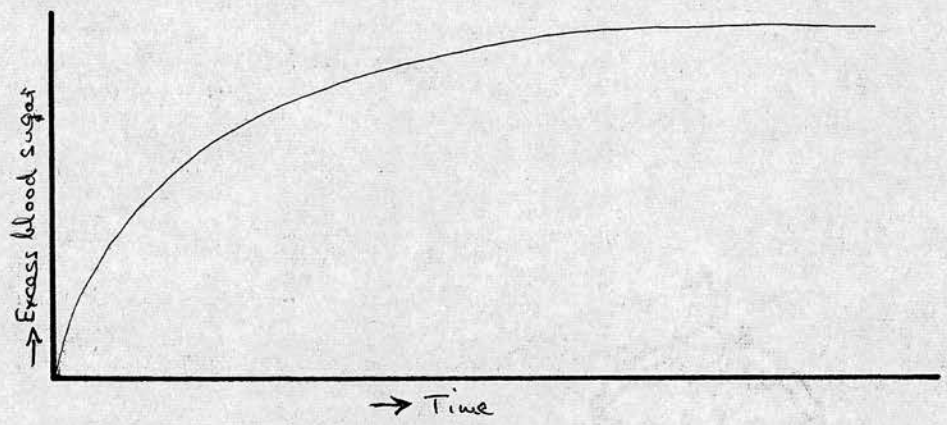

Figure II. Graph of excess blood sugar and time for a continuous slow infusion (after Jokipi and Turpeinen, 1954).

From results obtained in this way these authors derived a formula similar to the foregoing but including a factor, v, representing the volume of glucose distribution. Now the rate of change of glucose concentration is the rate of infusion (ρ) divided by the volume of distribution (v), or $\frac{ds}{dt} = \frac{\rho}{v}$. Therefore if glucose is simultaneously disappearing from the blood by a first

order or monomolecular reaction (that is, at a rate depending on the amount present) the net increase of blood glucose is expressed by $\frac{ds}{dt} = \frac{f}{v} - ks$. If the concentration of glucose in excess of the fasting blood glucose is 0 at $t = 0$, this gives:

$$s = \frac{f}{vk} (1 - e^{-kt}) .$$

Hlad et al. (1956) also used a continuous infusion and compared it with the single injection technique. Both were equally satisfactory. They, like Jokipi and Turpeinen (1954), used the blood sugar excess value and incorporated the factor "v" into their formulae. They showed that v could be calculated by making use of a theoretical value, S_{eq}, (blood sugar at $t = \infty$). Thus for a continuous infusion,

$$S_{eq} - S = (S_o - S_{eq}) e^{-kt} \text{ and } v = \frac{R_1 S_1}{k(S - S_f)}$$

where, R_1 = Rate of glucose infusion,

S_1 = concentration of glucose infusion,

S_f = fasting blood sugar.

Or for a single injection, $S - S_{eq} = (S_o - S_{eq}) e^{-kt}$

In the case of a single injection S_{eq} would correspond roughly to the S_∞ of Greville (1943). In the case of a continuous infusion S_{eq} would represent the equilibrium level, when glucose infused equalled glucose eliminated. Therefore on semilogarithmic paper straight line graphs would be produced in the case of a continuous infusion by plotting $S_{eq} - S$ against t and for a single injection by plotting $S - S_{eq}$ against t.

In a later publication Hlad and Elrick (1959) claimed that the above formulae which express exponential relationships did not depend merely on empirical observations (at best only approximations) but were accurate mathematical derivations from the actual blood sugar and time relationships reported by other investigators. This avoided a circular argument. These authors agreed with Greville (1943) that in normal subjects S_{eq} was always below S_f. In diabetics, however, S_{eq} was usually above S_f.

A further refinement was introduced by Marks and Bishop (1957) who calculated not only values for k (as defined earlier) but also what they termed the "mean net rate of glucose disappearance". This was defined as the number of milligrams of glucose disappearing per unit volume of blood per unit time and was given by:- $k \times S_{av}$, (where S_{av} = average total blood sugar concentration during the test). S_{av} was calculated by the formula:-

$$S_{av} = \frac{S_o(1 - e^{-kt})}{tk}$$

or (using excess blood sugar values over the fasting level):-

$$S_{av} - S_f = \frac{(S_o - S_f)\ (1 - e^{-kt})}{tk}$$

These authors reported reduced values for both "k" and "mean net disappearance of glucose" in a variety of malignant disorders. In view, however, of the close correlation between these two factors no additional information would seem to be gained by calculating anything other than "k" alone.

Macho and Licko (1957) calculated glucose clearance by the formula

$$\frac{Ik}{S_o - S_f}$$

where I = total glucose injected minus total glucose lost in the urine during the 60 minutes following injection.

As already stated above, however, urinary loss of glucose is so small during a normal IVGTT that this formula seems an unnecessary complication.

"Half" time.

Finally Lundbaek (1962) revived the simplified formula for k using the "half" time. This is the term given to the time taken for the blood sugar to halve itself during the course of an IVGTT. It had already been used by Amatuzio et al. (1953) and Jokipi and Turpeinen (1954) among others.

If we take the simple exponential equation,

$$S = S_o e^{-kt},$$

then let S_1 be the blood sugar at time t_1

and let S_2 at t_2 be $\frac{1}{2} S_1$ or $\frac{S_1}{2}$.

Let T = the interval between S_1 and S_2, that is, the half time.

Then, substituting, we derive:-

$$\frac{S_1}{2} = S_1 e^{-kT}$$

$$\text{or } \frac{1}{2} = e^{-kT}$$

$$\text{or } \log_e 1 - \log_e 2 = -kT$$

$$\text{or } k = \frac{\log_e 2}{T} = \frac{0.693}{T} \text{ (approx.)}$$

This method has the merit of simplicity. A straight line is usually

drawn by eye through a series of points plotted on semilogarithmic paper and the mathematics is reduced to a minimum. Inevitably, however, accuracy is sacrificed and this is a disadvantage if the IVGTT is to be used definitively in diabetes as well as diagnostically.

Triple Tolerance Test

In some ways comparable to the one-hour two-dose test of Exton and Rose (1934) was the suggestion of Soskin (1944) of a triple IVGTT. In this test three doses of 25 grams glucose were given intravenously at two hour intervals. In normal subjects the three successive two hour blood sugar levels were progressively lower but in patients with defects of carbohydrate metabolism (Soskin illustrates his report with the result of such a test on a hypopituitary subject) the two hour blood sugars become progressively higher.

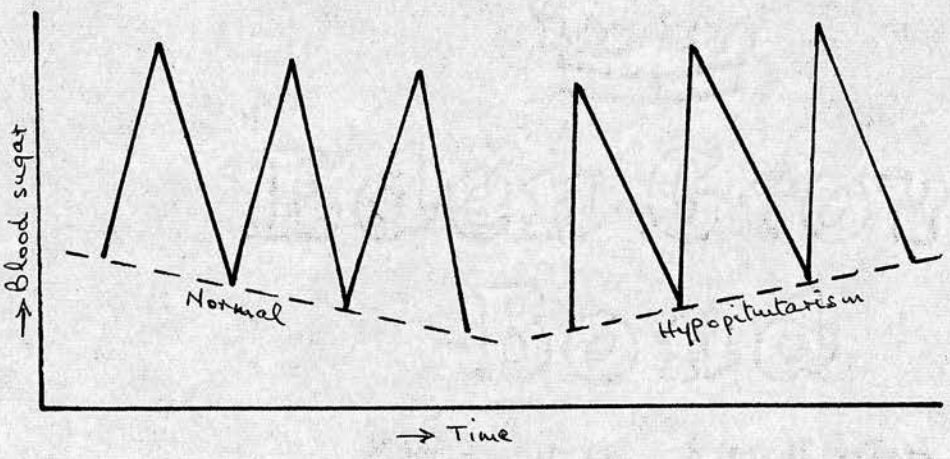

Figure III. Graph of blood sugar and time for the triple tolerance test (after Soskin, 1944).

This test, however, is lengthy, tedious and seems to offer no advantages of accuracy over the normal IVGTT.

Cortisone IVGTT

In view of the apparent success of the cortisone OGTT it is rather surprising to find so little mention of a cortisone IVGTT in the literature. Duncan (1956b) reported its satisfactory use in the prediction of two prediabetics by a lowering of the k values after cortisone but Holten et al. (1957) and Nilsson (1962) found no difference between the results in normal subjects and diabetic suspects. Bastenie et al. (1954) actually recorded an improvement in k values in their subjects after six weeks treatment with cortisone in a total dose of 10 grams. This test certainly merits more detailed study than it has received so far.

Comparison of OGTT with IVGTT

Both these procedures are equally liable to be affected by all the physiological variables previously mentioned with the exception of those relating to gastrointestinal absorption. This, however, is a very important exception. Glucose administration can be timed precisely in the IVGTT with no additional risks apart from the very rare occurrence of chemical phlebitis. Furthermore, the subject is saved what is often a rather nauseating draught of concentrated glucose and, if anything, the IVGTT takes less time than the OGTT.

Not only is the IVGTT preferable on practical grounds but it has certain advantages in respect of its interpretation. The chief of these is the ability to express an individual's status regarding his carbohydrate metabolism in one figure - the k value. This contrasts with the doubt that sometimes arises with an OGTT blood sugar curve where three factors - fasting blood sugar, peak rise and time to return to the fasting level - have to be considered. In all published reports of OGTT series a proportion of individuals so tested are found to have only one of these three factors in the abnormal range or who are slightly abnormal without being definitely diabetic. There is, of course, no clear dividing line between normality and abnormality and with any diagnostic test a proportion of those tested will fall into the "doubtful" range. It seems likely, however, that a test with only one criterion will result in fewer doubtful results than one with three criteria. Thus, provided the ranges for normality and

abnormality have been determined, the IVGTT may be used not only for diagnosis but also for definition - all k values above a certain figure being normal and those below it being abnormal.

Lundbaek (1962) has further recommended that the k value be used to evaluate the degree of diabeticity for a given individual. The results of the present study do not, however, suggest that this is a valid procedure. Many subjects in this series who were clinically very mild diabetics had k values less than others with clinically more severe diabetes (judged by insulin requirements, stability and liability to ketosis). Furthermore, the number of possible variables is so great that GTT's (of any type) may produce different results at different times regardless of the "diabeticity" of the patient. However, while the k value is of only limited use in determining an individual's diabeticity in any absolute sense, it may nevertheless be used thus in a relative sense for research or other purposes. For example, the effects of various treatments on the k value may be studied under controlled conditions.

Dupré (1964) and Elrick et al. (1964) showed that the rate of disposal of intravenous glucose is increased after prior administration of oral glucose. Balsano et al. (1964) and McIntyre et al. (1964) suggested that this might be due to a humoral substance released from the jejunal wall during glucose absorption, facilitating the release of insulin from the pancreatic islet cells.

One possible hormone responsible for such an effect is secretin, shown by Boyns et al. (1967) and Persson et al. (1967) to have a marked insulinotropic action. This, however, is only so if exogenous secretin is given, the (more physiological) stimulation of endogenous secretin by duodenal infusions of citric acid producing no significant alteration in plasma insulin levels (Boyns et al. 1966, Mahler and Weisberg 1968). Another contender for the role of insulinotropic hormone is pancreatic glucagon (Samols et al. 1966, Ryan et al. 1967, Turner et al. 1967).

Whatever hormone is finally credited with this action, however, the fact remains that orally administered glucose produces a higher plasma insulin response than that produced by intravenous glucose. This in turn leads to a more rapid fall of blood glucose levels and therefore to greater "tolerance" during an OGTT. The same tendency would presumably result in lower k values (representing poorer tolerance) in a given IVGTT than would be otherwise expected from an OGTT in the same subject. Thus a number of borderline or suspect diabetics (on an OGTT) might be brought more clearly into the diabetic range on an IVGTT. This advantage, if it can be called such, is seen in the results of the present series of tests and may be of some value in the study of this intermediate group.

In this connection, however, it is of interest to note that Moyer and Womack (1950) found that although the IVGTT was very <u>specific</u> it was too <u>insensitive</u> - that is, a normal result was

produced in two diabetics diagnosed by an OGTT. It all depends, perhaps, upon what one calls "normal".

As with any new diagnostic test there is the danger of a circular argument. The new test (or the interpretation of it) seems to divide neatly between diabetics and non-diabetics. But the criteria for this classification are older tests and one could argue that the old tests are therefore as good as the new. In these circumstances theoretical considerations must be applied, at least partly, in the evaluation of any new test designed to improve the accuracy (though not necessarily those designed to improve the practicability) of an older test (West and Wood 1959). The theoretical basis for the IVGTT has been described in the preceding pages and is seen to offer a much more accurate measure of carbohydrate metabolism than the OGTT. From the practical point of view also, the results of many comparative series confirm the superiority of the IVGTT and its use is strongly recommended in preference to the OGTT (Jorgensen 1926, Lennox 1927, McKean et al. 1935, Baird and Duncan 1959, Lundbaek 1962).

Other Diagnostic Tests

Although the GTT in some form has for many years held pride of place in the diagnosis of diabetes a great many other procedures have been used with varying degrees of success from time to time.

Respiratory quotient

Rabinowitch (1925) measured the respiratory quotient in subjects following the intravenous injection of dextrose. He found that it rose less, or even fell slightly, in diabetics as compared with non-diabetics. Thayson (1929), however, using the same method, found the same rise of respiratory quotient after dextrose injections in normal subjects and in those with steatorrhoea - a group whose glucose tolerance is usually reduced (Fairley 1936, Ross and Tonks 1938, Frazer et al. 1952).

This technique has theoretical possibilities. It is probable, however, that any procedure depending on the measurement of respired gases would be subject to at least as many variables as a GTT and hence be very inaccurate. It is no longer used as a diagnostic test.

Serum phosphorus

Wertheim et al. (1954) found that the serum phosphorus fell less in diabetics than in normal subjects during the course of an IVGTT. Kritzer et al. (1956) who confirmed these findings noted also that as phosphorus is utilized in the peripheral rather than the

hepatic metabolism of glucose, measurement of its response to injected glucose might distinguish a true diabetic from those individuals with liver disorders and failure of glycogen metabolism. However, the same authors found a great overlap in the results obtained from diabetics and normal subjects and their observations are therefore more useful statistically than diagnostically.

Plasma insulin

Since that time, however, much work has been carried out on aspects of glucose metabolism other than the fluctuations of actual blood glucose itself. Particularly is this so in respect of plasma insulin. Vallance-Owen et al. (1955) studied plasma insulin levels in obese non-insulin-dependent diabetics and found a higher than normal fasting level but a smaller than normal rise following glucose. This pattern has been confirmed by Berson and Yalow (1961), Phear (1962), Hales and Randle (1963) and Hales et al. (1965). Similar responses to glucose loads are seen also after myocardial infarction (Nikkila et al. 1965), in obese non-diabetics (Phear 1962) and in likely pre-diabetics (Steinke et al. 1963, Pfeiffer and Zeigler 1965). In some ketotic insulin-dependent diabetics detectable insulin activity may be very low or absent (Vallance-Owen et al. 1955, Taylor 1963). It may be that a clearer assessment of the diabetic and suspected pre-diabetic is now possible by studying the plasma insulin response as well as the blood sugar levels during a GTT (Samols and Marks 1965, Lister 1966, Johansen and Lundbaek 1967).

Similar information may also be obtainable from urinary insulin measurements (McArthur and Stimmler 1966, Lieberman 1968).

Non-esterified fatty acids

Hales and Randle (1963) observed that fasting levels of non-esterified fatty acids, as well as serum insulin, were frequently raised in mild diabetics. Unfortunately further work, while confirming this, showed that there was too wide a scatter of values between normal and diabetic subjects for this finding to have real diagnostic importance in any particular individual (Hales et al. 1965).

Skin surface glucose

Miller and Ridolfo (1960) suggested that measurement of the skin surface glucose by means of a glucose oxidase test paper held between the fingers might be a satisfactory and simple screening procedure. West et al. (1963), however, found it entirely without value in differentiating diabetics from normal individuals.

Tolbutamide tolerance test

In 1956 Mirsky et al. published a report of the effect of oral tolbutamide on the blood sugar in normal and diabetic subjects. They found that although many diabetics had as great (or occasionally greater) hypoglycaemic responses the mean levels were different for the two groups and in diabetics the fall tended to be slower. These observations led to the development of the tolbutamide tolerance test

introduced by Unger and Madison (1957). These authors injected tolbutamide intravenously and found in normal subjects a sharp fall of blood sugar to a nadir at between 20 and 40 minutes after the injection and a subsequent slower rise to a level usually about 75% of the starting figure by 60 minutes. In diabetics, although the same level was often reached by the end of one hour, there was usually no intervening nadir, the blood sugar falling gradually throughout the test period.

The same technique was also used by others who found it satisfactory, both for the diagnosis of diabetes (Kaplan 1961) and the prediction of pre-diabetes (Dolger et al. 1962) although it was less suitable in the case of children (DiGeorge and Chianovitch 1963). Boshell et al. (1963) also used it but preferred to give the tolbutamide by mouth, claiming that this method reduced the risk of hypoglycaemic symptoms which occasionally complicated the intravenous test.

Kaplan (1961), however, noted that the tolbutamide tolerance test was often normal when the OGTT and IVGTT were abnormal and especially was this so if the subject being tested was obese. This last observation is perhaps not surprising in view of the fact that individuals with early diabetes, pre-diabetes or even obese non-diabetics frequently have raised serum insulin levels (Phear 1962, Steinke et al. 1963, Hales et al. 1965). Although the increased plasma insulin is usually in an inactive form (Camerini-Davalos et al. 1963, Steinke et al. 1963) it may evidently on occasion be active, even to the extent of producing spontaneous hypoglycaemia (McClellan

and Wardlaw 1932, Skillearn and Rynearson 1953, Seltzer et al. 1956). Such insulin activity could lead to normal or near normal blood sugar curves in the tolbutamide tolerance test and false negative results in the very group (mild diabetics and pre-diabetics) where early diagnosis might be so important. This weakness has been demonstrated by Conn and Fajans (1961) and Drury and Timoney (1963) who confirmed the inferiority of the tolbutamide tolerance test to the cortisone OGTT in the diagnosis of early diabetes.

Prednisone induced glycosuria

Joplin et al. (1961) returned to the measurement of glycosuria for diagnosis in their prednisone glycosuria test. In this test 20 mg of prednisone is given at 12 noon, 4.00 p.m. and 8.00 p.m. and the subject is then fasted until 6.00 a.m. the next morning. From 10.00 p.m. to 6.00 a.m. all urine is collected and blood is taken for blood sugar estimation at 12 midnight and 1.00 a.m. Joplin et al. (1961) found that normal subjects lost less than 60 mg of glucose per hour in their urine during the test period, while all the mild diabetics in their series and 25 out of 47 suspected pre-diabetics passed more than this quantity. Figures for the night blood sugars were:-

Normal subjects, 90 - 133 mg per 100 ml (mean, 111);

Suspect pre-diabetics, 115 - 166 mg per 100 ml (mean, 141).

This is a simple procedure and useful for screening diabetic suspects especially, for example, during pregnancy when the subjects

under investigation are in hospital (Davey et al. 1961). Difficulties may be encountered, however, (especially in this particular group) with cases of lowered renal glucose threshold and the test does not seem to have the same degree of specificity that can be claimed for the cortisone GTT.

Experimental work

There remain a number of other procedures suggested during the course of experimental work in this subject. These have as yet not reached the point of becoming actual diagnostic tests and only brief mention need be made.

They include the pyruvate tolerance test (Moorhouse 1964), observations on the effect of glucagon (Butterfield et al. 1960) and metyrapone (Mirouze et al. 1962) on normal and diabetic subjects, the prediction of hereditary diabetes in hamsters by a rise in the level of serum α - 2 globulin fractions (Green et al. 1963) and studies in urinary albumen (Keen and Chlouverakis 1964) or steroid (Charro-Salgado et al. 1968) excretion patterns.

It is possible that from this and other work currently in progress a more satisfactory diagnostic test than the GTT will sooner or later emerge. For the present, however, one or other form of GTT remains the best criterion.

PRESENT STUDY

Introduction

(N.B. Although the following arguments are strictly concerned with blood glucose as such, earlier workers here quoted have, in fact, in most cases based their views on observations of the blood "sugar". In spite of apparent inconsistencies in the line of argument, therefore, these two terms are used here in exactly the same way as in other sections of the thesis).

It will be apparent from the preceding section that there exist at least three schools of thought regarding the best way of considering blood sugar levels during an IVGTT. All agree that an exponential relationship appears to exist (at least approximately and for some part of the test) between the blood sugar and the time after glucose injection. Some workers, however, have considered that the rate of fall of blood sugar is proportional to the "total" sugar (that is, the actual blood sugar level measured at a given moment) and have therefore used these figures for the calculation of k (Ikkos and Luft 1957, West and Wood 1959, Lundbaek 1962). This value may be called "k (total)".

Others have preferred to use "excess" sugar (that is, either the difference between the observed blood sugar (S) and the fasting level (S_f) (Amatuzio et al. 1963, Duncan 1956a) or the difference between

the observed blood sugar and some other level (S_∞ or S_{eq}) lying rather below the fasting blood sugar (Greville 1943, Hlad et al. 1956)), arguing, instead, that the rate of blood sugar fall is proportional to these values. In both cases the term "k (excess)" is substituted.

These three views may be represented by three formulae, all of which have already been introduced earlier,

<u>viz.</u> $\log S = \log S_0 - kt$ .. .. 1.

$\log (S - S_f) = \log (S_0 - S_f) - kt$ .. .. 2.

$\log (S - S_\infty) = \log (S_0 - S_\infty) - kt$ .. .. 3.

It is readily seen that equations "2" and "3" differ from "1", only by constant terms, respectively S_f and S_∞, which are subtracted in each case from the observed blood sugar figure, S.

It is difficult to compare these three forms of the simple exponential equation directly as each depends on different theoretical hypotheses and there is no constant proportional relationship between them. What is certain, however, is that the inclusion of a constant term into the equation in this way does not result merely in a shift of the blood sugar graph bodily up or down but affects the shape and slope of the line also.

In Figure IV a straight line A-A has been drawn across semi-logarithmic graph paper to represent an imaginary IVGTT blood sugar slope and points have been marked along it to represent blood sugar levels at definite time intervals. Best fitting straight lines

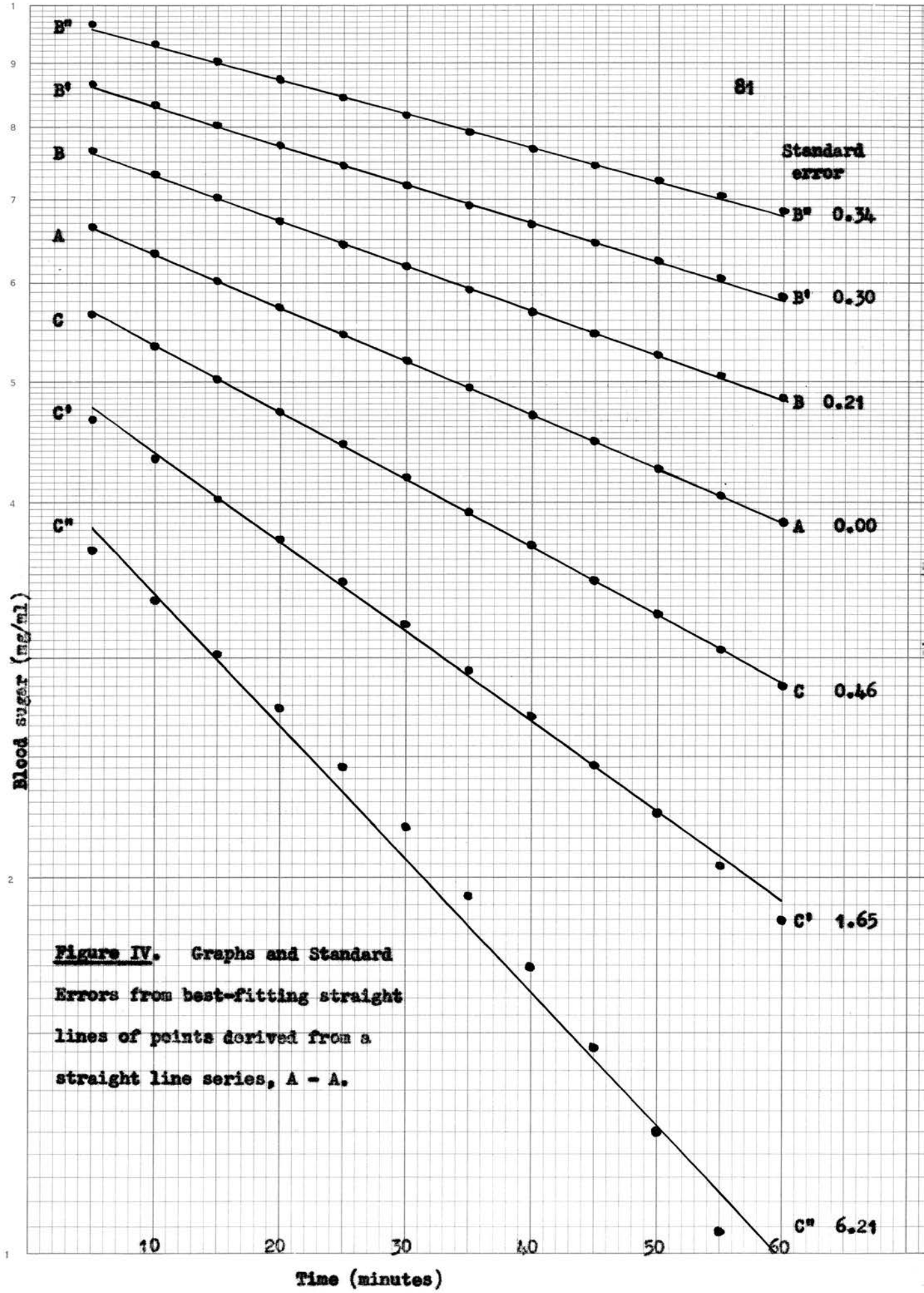

Figure IV. Graphs and Standard Errors from best-fitting straight lines of points derived from a straight line series, A - A.

B-B, B'-B', and B"-B" have been drawn through points at the same time intervals but respectively 100, 200 and 300 mg per 100 ml in excess of comparable points along A-A. Likewise, best fitting straight lines C-C, C'-C' and C"-C" have been drawn through points respectively 100, 200 and 300 mg per 100 ml below comparable points on A-A. The Standard Error (SE) of these points from the best- fitting straight lines has been calculated and shown in each case. It will be seen that within the range of variation illustrated the greater the displacement of a line from A-A in either direction, the greater the slope alters and the larger the SE becomes.

The implication of this would seem to be that whereas a slope representing an exponential relationship between two functions may be moved up or down by adding or subtracting constant terms, there is only one position (within the range illustrated, at least,) where the points fall actually in a straight line; in all other positions the points will be scattered to a greater or lesser degree from straight lines fitted to them. In an actual IVGTT, of course, it is unlikely - for a variety of technical and physiological reasons - that a perfect straight line would ever be obtained and because of the calibration of semi-logarithmic paper any scatter of points about a best-fitting straight line is less obvious (visually) the higher up the scale it lies. Nevertheless, the exact degree of scatter about any line can be determined by calculation of the SE of the observed points from that line.

(The SE is given by the formula:- $SE = \frac{(S - S_1)^2}{n - 2}$

where $S - S_1$ represents the difference between the observed blood sugar level at a given moment and the calculated blood sugar level lying on the best-fitting line at the same time,

n = the number of blood sugar readings.)

Thus the SE of a series of points from any line may be taken as an index of the goodness of fit of that line.

A series of graphs may therefore be drawn for any set of blood sugar readings obtained during an IVGTT using all the various forms of the exponential equation ("1", "2", or "3" above). As explained, a perfect straight line is unlikely to result from any actual IVGTT but one of the three equations will be found which provides a better straight line fit than the others. This would be the graph with the smallest SE.

In the present context, supporters of the view that "total" blood sugar should be used for calculation of k claim that equation "1" would produce the best straight line available (illustrated in Figure IV by line A-A). If this is so it follows that deduction of S_f (or of some other value for S_∞) from the observed figures would move the whole slope downwards toward C-C, C'-C' or C"-C" with consequent increase of SE. On the other hand, those who claim that equations "2" or "3" produce the best straight lines would argue that use of "total" blood sugar results in lines tending towards B-B, B'-B' or B"-B", again with increasing SE.

If S_∞ in equation "3" is equal to zero then equation "3"

becomes equation "1". Similarly, if $S_\infty = S_f$ then equation "3" becomes equation "2". Thus by allotting various arbitrary values to S_∞ in a given IVGTT that value may be found which produces the graph with minimum SE.

If minimum SE is obtained when $S_\infty = 0$ it follows that "total" blood sugar values should be used for calculation of k. If, on the other hand, a better fit is produced when $S_\infty = S_f$ (or some other value lying between 0 and S_f), then "excess" blood sugar values are to be preferred.

One further possibility is that minimum SE may be obtained when S_∞ is negative. This would mean the addition of a constant figure to all observed blood sugar readings rather than the subtraction proposed by users of "excess" blood sugar values. This point is discussed on pages 162 and 170 ff.

In any event, calculation of SE for best-fitting straight lines drawn through series of points derived from a given IVGTT by substituting different values of S_∞ will determine that value of S_∞ which gives the best fit. Thus, preference for equation "1", "2" or "3", that is, for "total" or "excess" blood sugar (or, in the present study, blood glucose) may be established.

It may be argued, however, that only the central part of the blood sugar slope (that is, that part relating to true metabolism of glucose) should be used for calculation of k. In the present study this practice has been adopted so far as the later stages of the test are

concerned and blood glucose values less than 25 mg per 100 ml in excess of the fasting level have been ignored. It is probable that this degree of limitation is unnecessary as in many cases good fitting straight lines can be drawn to include blood glucose points right down to the original fasting level. Nevertheless some arbitrary limit must be fixed and this, while possibly excluding some points that could be included, is at least fairly certain to exclude any points that should not be included. All points 25 mg per 100 ml or more in excess of S_f are referred to below as "valid" points.

Consideration of the earlier part of the slope is a little more difficult. If the fall of blood glucose is steeper in the first few minutes than during the later parts of the test, k values based on all blood glucose readings will tend to be higher than if only the central points are used. If, however, a true exponential relationship between blood glucose and time exists for the central part of the test, then during that time the graph will be a straight line. If there is a straight line section in an IVGTT graph it may therefore be found as follows: k could first be calculated for the slope of the best-fitting straight line through all the blood glucose readings available (that is, every 5 minutes, starting 5 minutes after glucose injection). It could then be recalculated using all except the first (5 minute) reading; then again, omitting the first two points, and so on until a stage is reached when omission of further points produces no further change in k. At this stage, presumably, a straight line slope is present. In practice, again, there will

always be a certain scatter of points and omission of any one is liable to alter the value of k for the best-fitting straight line through the remainder. However, in spite of some continuing variability of k, it may be possible to decide approximately at what stage a reasonably steady value has been reached.

These two aspects of the IVGTT form the main part of the present study. Two further subsidiary objects have also been mentioned already on p.2, namely (a) to establish, if possible, a simpler test of comparable accuracy using fewer readings and (b) to determine (using the simpler test) the ranges of normality and abnormality for the IVGTT to be used both for the diagnosis and the definition of diabetes.

Subjects and Methods.

For the main study twenty four subjects were selected (cases 1 - 24, see below). There were twelve diabetics and twelve non-diabetics. Of these, three were healthy volunteers; the rest were all in-patients at the Adelaide Hospital, Dublin. None was suffering from any endocrine disorder apart from diabetes and the majority were ambulant.

The average age of the group as a whole was 56.9 years (range 22 - 77); that for the diabetics, 63.5 years (range 51 - 77) and for the non-diabetics, 50.0 years (range 22 - 77). The possible bearing on the results of the unmatched age structure for the two groups is discussed on page 168. There were 17 males and 7 females.

Preparation

The question of an adequate pre-test carbohydrate intake has been discussed in the previous section (p. 44). In the light of this evidence it was felt unnecessary to insist on the very high (300 grams or more) carbohydrate diets recommended by some workers (Conn 1940, Unger 1957), which would be excessive for many bed patients. In the present series, therefore, all subjects were already taking a full diet containing at least 175 grams of carbohydrate per day and this was not changed. Several days were allowed to elapse after any surgical procedure or acute illness and any anti-diabetic treatment was stopped at least 36 hours (or, in the case of those patients

receiving chlorpropamide, at least 48 hours) before a GTT. Even 48 hours may not be long enough to eliminate all significant effects of chlorpropamide in those patients receiving that drug, but a longer interval without treatment was not thought to be clinically justifiable. The names of patients receiving chlorpropamide are therefore marked with an asterisk in all relevant tables and their results discussed with this in mind. In the case of those patients newly discovered to have diabetes, GTT's were performed before starting any antidiabetic treatment. There was no patient in this series currently receiving protamine zinc insulin.

All subjects apart from established diabetics had a standard 50 gram OGTT performed during the few days just before or after the IVGTT. This test was done after an overnight fast of approximately 12 hours. Venous blood and urine samples were collected fasting and at 1 and 2 hours after 50 grams of glucose in 180 ml of water by mouth. Blood sugar was estimated by the method of Folin and Wu (Harrison 1958) and glycosuria by "clinitest" tablets.

With this method the limits of normality were taken as follows:-

(a) Fasting blood sugar less than 120 mg per 100 ml,

(b) Peak blood sugar not exceeding 180 mg per 100 ml,

(c) Return to less than 125 mg per 100 ml by 2 hours.

An individual whose test figures lay below all three criteria was considered non-diabetic; if any two were exceeded he was regarded as diabetic. Diabetics were further subdivided into two grades (see p.9), viz. mild (7 patients) or moderate (5 patients).

Brief details of each patient are included in Table VII and this information is expanded in the Appendix.

It is necessary to explain that although the present study may incidentally illustrate some of the previously described advantages of the IVGTT over the OGTT, it cannot be used to prove this point because "blood sugar" was estimated in venous blood by the method of Folin and Wu for the OGTT but as true glucose in capillary blood for the IVGTT. This apparent absurdity was dictated by the fact that whereas IVGTT's were performed by the writer personally, OGTT's were nearly all done as routine investigations by the methods currently used in the hospital. As the object of this study was not the direct comparison of these two tests, repeated OGTT's using true glucose methods were not considered justifiable and routine OGTT's were used merely as a convenient means of grading the subjects.

Intravenous glucose tolerance test.

After an overnight fast capillary blood was obtained by finger-prick for blood glucose estimation. 50 ml of 50% dextrose solution, to which had been added about 1,000 units of heparin to prevent thrombophlebitis, was then injected slowly and evenly into an ante-cubital vein over a period of 4 minutes timed with a stop watch. Further blood samples were obtained at 5 minute intervals for 50 minutes, with a final sample at 60 minutes, timed from the mid point of the glucose injection. In one or two instances blood samples were not taken exactly at these intervals. In such cases

the actual times were noted and the final calculations adjusted accordingly. Urine was not collected. Because of possible distortion of the curve by homeostatic mechanisms blood glucose readings within 25 mg per 100 ml of the fasting level were ignored in the calculation.

Reagents.

Reagents were obtained from a special kit (reference TC-M-1 article No. 15982, Messrs. Boehringer and Co., Mannheim) for the estimation of true glucose as follows:-

1. Buffer/enzyme powder containing 0.12 M phosphate buffer (Sodium ortho-phosphate dihydrogen, NaH_2PO_4, and sodium ortho-phosphate monohydrogen, Na_2HPO_4, at pH7), 6 mg peroxidase and 67.5 mg of glucose oxidase were completely dissolved in 150 ml of distilled water.
2. Chromogen (13.2 mg o-dianisidine hydrochloride) was dissolved in 2.0 ml of distilled water.
3. "Glucose reagent" was obtained by mixing one volume of chromogen with 100 volumes of buffer/enzyme solution freshly before each test.
4. Glucose "standard" solution containing 91 μg glucose per ml..

Blood glucose estimation

0.1 ml of each blood sample obtained was mixed in separate tubes with 1 ml of 0.33 M perchloric acid to precipitate the proteins. After centrifuging, 0.2 ml of the supernatant from each tube was pipetted

into further tubes, 5 ml of "glucose reagent" was added and thoroughly mixed. 0.2 ml of glucose "standard" solution and 0.2 ml of distilled water (as control) were added respectively to two further tubes containing 5 ml "glucose reagent" and the whole set allowed to stand for exactly 35 minutes. At the end of this time colour changes (optical density) were read on an EEL colorimeter, using a 624 green filter, comparing the test solutions with the known glucose "standard". Blood glucose was calculated by the formular-

$$\frac{\text{Colorimeter reading of test solution}}{\text{Colorimeter reading of glucose "standard"}} \times 100 \text{ (in mg/100 ml.)}$$

Reliability criteria

1. Accuracy The series of tubes for each test also included one tube containing a solution of known glucose content ("Lab-trol" or "Patho-trol": Dade controls, Armour Pharmaceutical Co. Ltd.) This was treated in exactly the same way as all the other tubes. Using the above method for glucose estimation figures obtained for the glucose concentration of these control solutions differed from the actual concentration by an average of 2.65% $\pm$ SD 2.4.

2. Precision On several occasions blood glucose estimations were carried out in duplicate or triplicate on the same series of tubes in a given IVGTT. Results for such double or triple estimations varied from each other by an average of 0.35% $\pm$ SD 1.1.

3. Specificity. The method described is specific for d - glucose with the exception that elevated blood levels of glutathione or vitamin C may cause falsely low readings. The manufacturers of the special kit used claim an average error margin of less than ± 5%.

4. Sensitivity. This is limited by the accuracy with which one can read an EEL colorimeter. Inevitably it is less in the upper part of the scale. With very high blood glucose levels, however, blood samples were diluted so as to give colorimeter readings near the middle of the scale. In this way the smallest change in readings which could be accurately appreciated represented about 3 mg glucose per 100 ml.

Procedure

Exponential relationship

Blood glucose (in mg per ml) was plotted against time (in minutes) on semilogarithmic graph paper and best-fitting straight lines, using all valid points, were calculated by the method of least squares, viz.

$$\Sigma(\log S) = nS_o + k\Sigma(t)$$

$$\Sigma(\log S.t) = S_o\Sigma(t) + k\Sigma(t^2)$$

(where S = blood glucose at time, t,

S_o = theoretical blood glucose at t = 0, found by extrapolation,

n = total number of blood glucose readings,

k = a constant, representing the slope).

In this way, k was found for each individual.

Exponential relationships are customarily expressed as functions of "e" by use of Naperian logarithms. Calculations in the present study have all been done by logarithms to base 10 and the final results multiplied by a factor of 2.303 to comply with this practice. All values for k and SE throughout (including all relevant Tables) have been further multiplied by 100 for convenience.

Graphs obtained in the way described represent the special case of the equation, $\log (S - S_\infty) = \log(S_0 - S_\infty) - kt$ when $S_\infty = 0$. In other words, they are based on the assumption that the rate of fall of blood glucose in an IVGTT is proportional to the <u>total</u> amount of glucose present.

In view of the inevitable slight scatter of points about these straight lines, the SE was also calculated in each case.

For each subject the values for k and SE were also calculated for further best-fitting lines obtained by means of a series of arbitrary values for S_∞ ranging from 10 to 100 by increments of 10 and also the special case where $S_\infty = S_f$.

In addition to the foregoing 24 subjects the mean blood glucose values at stated time intervals were also determined for the 12 diabetics as a group and the 12 non-diabetics as a group. These two sets of mean blood glucose values are referred to below as "cases" (Nos. 25 and 26 respectively for diabetics and non-diabetics - see Appendix, pp. 244 and 245 for details). k and SE were calculated for these two "cases" in the same way as that described for cases 1 - 24.

For comparison, mean blood sugar values at stated time intervals were also calculated from figures published in four other reports, namely Greville (1943) Amatuzio et al. (1953), Duncan (1956a) and Ikkos and Luft (1957). Sets of mean values thus obtained are likewise referred to below as "cases" (see Appendix pp. 246 - 252 for details). These reports refer to the following groups of patients:-

Author	Number of subjects	Type of subject	Case No.
Greville (1943)	6	Non-diabetics	27
Amatuzio et al. (1953)	26	Diabetics	28
	70	Non-diabetics	29
Duncan (1956a)	15	Diabetics	30
	20	Non-diabetics	31
Ikkos and Luft (1957)	47	Diabetics	32
	16	Non-diabetics	33

These reports all refer to blood "sugar" rather than blood glucose and therefore should not, strictly speaking, be compared with cases 1 - 24 or cases 25 and 26. However, they are the only other detailed IVGTT figures available for comparison, so far as the present writer has been able to discover, and they have therefore been included.

Accordingly, the same calculations for the determination of k and SE have been made with cases 27 - 33 as described above for cases 1 - 26. The results obtained for cases 27 - 33, here and in subsequent sections, are, however, commented upon separately in the text.

Results from the calculations referred to above - for all cases - are shown in Table IV.

In view of theoretical objections to the use of blood sugar or blood glucose points prior to the 20th minute after glucose injection the whole calculation was repeated in each case (including Nos. 25 - 33) using only those points from 20 minutes onwards. Results are shown in Table V.

Section of slope to be used

Having obtained the values of k for the best-fitting straight lines when $S_\infty = 0$, using all valid points in each case, k was recalculated (again taking $S_\infty = 0$) omitting the first blood glucose reading. This process was repeated, this time omitting the first two readings, then again, omitting the first three readings and so on several times until only the last four or five points were used. In each case and for each section of the IVGTT blood glucose slope used the SE from best-fitting straight lines was also calculated. Results are shown in Table VI.

Exactly the same procedure was used for cases 25 and 26 and for cases 27 - 33, all these results being included in Table VI.

Simple test

As described above k values were obtained from best-fitting straight lines based on all valid points, omitting those points prior

to the 20th minute after glucose injection. These were compared with k values obtained from best-fitting straight lines based on the 20, 40 and 60 minute points only. In six cases the blood glucose had fallen to within 25 mg per 100 ml of the original fasting level by the 60th minute. In these cases, therefore, k was calculated from the 20 and 40 minute points only. (As there were only two points, the SE was, of course, zero).

Values for k were calculated both for "total" and "excess" (over S_f) blood glucose. In each case and for both k (total) and k (excess) the differences between k values using all except the first three valid points (k) and values obtained by using only the 20, 40 and 60 minute points (k') were expressed as a percentage change from the mean of the two values $\left(\frac{k + k'}{2}\right)$

viz. $$\frac{\text{Difference between k and k' x 2}}{k + k'} \times 100$$

Only cases 1 - 24 have been treated in this way. Results are shown in Table VII.

Range of k values

Using the simple test as described a further 100 subjects (cases 34 - 133) were studied, comprising 50 diabetics and 50 non-diabetics. Four subjects were healthy volunteers. The rest were in or out patients at the Adelaide Hospital, Dublin. There were 61 men and 39 women. The classification into diabetics and non-diabetics, preparation, IVGTT technique and calculation of individual k values

were exactly the same as described for the longer test except that blood glucose was estimated only at the 20th, 40th and 60th minute after glucose injection. In a few tests blood samples were not taken precisely at these times. In such cases the actual times of collection were noted and the calculation of k adjusted accordingly.

The diabetic group was further subdivided according to severity, viz. mild (35 patients), moderate (9 patients) and severe (6 patients). The number of subjects, by age, for each subgroup is shown in Table III.

A large number of all cases studied were under investigation or treatment for varying degrees of peripheral vascular disease but many other disorders were also represented. As before, no patient had any endocrine disorder other than diabetes and the majority were ambulant. Subjects were graded according to body build, either obese, average or thin.

Brief details of all patients are given in Tables VIII and IX and this information is expanded in the Appendix. The range of k values obtained in this series is shown in Figures XXXVIII and XXXIX.

Calculations were checked by I.B.M. computer. The machine used was IBM 1620, 20,000 digits of cold store, with paper tape and typewriter input and output and programmed using standard least squares.

	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Total	Mean age
Non-diabetics	2	8	5	8	10	11	5	1	50	49.0
Mild diabetics	-	-	1	3	6	14	7	4	35	64.2
Moderate diabetics	-	-	-	1	2	2	4	-	9	64.5
Severe diabetics	-	1	1	-	-	1	3	-	6	57.5
All diabetics	-	1	2	4	8	17	14	4	50	63.4
Total	2	9	7	12	18	28	19	5	100	56.2

Table III. Age distribution (in years) for subjects undergoing the simple IVGTT.

RESULTS

"Total" or "Excess" blood glucose

Table IV records the variation in SE from best-fitting straight lines through series of points obtained in each case by allotting a number of different arbitrary values to S_∞ in the formula,

$$\log (S - S_\infty) = \log (S_0 - S_\infty) - kt.$$

For this purpose all valid blood glucose readings have been included in the calculation. The actual fasting blood glucose level has been included in brackets beside the individual values for SE in the column headed "$S_\infty = S_f$".

It will be seen that in most cases an increase in the value of S_∞ is accompanied by a progressive increase in SE. In these cases, therefore, it would appear that the closest approximation to a straight line occurs when "total" blood glucose is used, that is, when $S_\infty = 0$.

In two cases, however, (Nos. 19 and 24) this progressive rise is not seen. In these cases the SE first rises then falls to a minimum and finally rises sharply again as S_∞ increases. The implication here, therefore, is that the "ideal" value for S_∞ (that is the value which gives the closest approximation to a straight line) lies above 0 and that the use of "excess" blood glucose is to be preferred. Of these two cases No. 19 shows that the SE when $S_\infty = S_f$ is greater than when $S_\infty = 0$, while in No. 24 the SE when $S_\infty = S_f$ is less than when $S_\infty = 0$.

Case No.	$S_\infty = 0$	$S_\infty = +10$	$S_\infty = +20$	$S_\infty = +30$	$S_\infty = +40$	$S_\infty = +50$	$S_\infty = +60$	$S_\infty = +70$	$S_\infty = +80$	$S_\infty = +90$	$S_\infty = +100$	$S_\infty = S_f$	(S_f)
1	4.39	4.52	4.67	4.83	4.99	5.17	5.36	5.56	5.78	6.01	6.25	6.86	(122)
2	2.26	2.34	2.42	2.51	2.60	2.71	2.81	2.93	3.06	3.23	3.48	3.48	(100)
3	1.10	1.13	1.17	1.21	1.25	1.31	1.39	1.49	1.64	1.86	2.17	2.17	(100)
4	3.07	3.13	3.20	3.27	3.34	3.42	3.50	3.58	3.67	3.76	3.85	12.10	(263)
5	2.52	2.62	2.74	2.86	3.00	3.15	3.31	3.49	3.69	3.91	4.16	10.59	(200)
6	3.33	3.42	3.50	3.60	3.69	3.80	3.92	4.05	4.21	4.40	4.67	4.50	(94)
7	1.92	1.98	2.03	2.09	2.16	2.22	2.30	2.38	2.47	2.58	2.70	2.79	(106)
8	4.58	4.70	4.83	4.97	5.12	5.27	5.43	5.60	5.77	5.96	6.16	6.57	(119)
9	1.70	1.80	1.91	2.02	2.16	2.32	2.49	2.70	2.94	3.23	3.57	3.15	(88)
10	4.43	4.53	4.64	4.75	4.87	5.00	5.12	5.26	5.40	5.54	5.69	6.82	(171)
11	1.19	1.23	1.27	1.31	1.36	1.41	1.46	1.52	1.59	1.65	1.73	6.17	(260)
12	1.66	1.70	1.74	1.79	1.83	1.88	1.93	1.98	2.03	2.09	2.14	2.32	(192)
13	6.15	6.41	6.71	7.07	7.52	8.11	8.93	10.13	12.03	15.29	19.38	14.59	(88)
14	1.79	1.94	2.13	2.35	2.64	3.01	3.50	4.19	5.19	6.75	9.41	7.58	(94)
15	3.84	3.93	4.02	4.12	4.22	4.32	4.43	4.55	4.67	4.80	4.93	5.00	(105)
16	2.89	3.15	3.46	3.84	4.32	4.93	5.72	6.79	8.29	10.50	14.09	9.28	(85)
17	3.66	3.81	3.98	4.17	4.37	4.59	4.84	5.23	5.45	5.84	6.33	5.48	(82)

Table IV. Variation of SE for different values of S_∞, using all valid points. (Cases 1 - 17)

Case No.	$S_\infty = 0$	$S_\infty = +10$	$S_\infty = +20$	$S_\infty = +30$	$S_\infty = +40$	$S_\infty = +50$	$S_\infty = +60$	$S_\infty = +70$	$S_\infty = +80$	$S_\infty = +90$	$S_\infty = +100$	$S_\infty = S_f$	(S_f)
18	1.69	1.88	2.11	2.41	2.78	3.27	3.93	4.83	6.13	8.09	11.33	6.29	(81)
19	4.30	4.34	4.35	4.35	4.32	4.26	4.17	4.09	4.15	4.74	6.74	4.50	(88)
20	6.55	7.01	7.56	8.22	9.03	10.04	11.35	13.10	15.57	19.32	25.69	17.23	(85)
21	5.38	5.61	5.86	6.16	6.52	6.99	7.67	8.72	10.58	14.27	23.02	11.94	(85)
22	2.11	2.15	2.19	2.23	2.27	2.31	2.35	2.40	2.44	2.49	2.55	2.64	(113)
23	2.75	2.85	2.97	3.09	3.22	3.37	3.53	3.72	3.95	4.23	4.63	3.53	(60)
24	6.31	6.43	6.54	6.61	6.64	6.58	6.39	6.01	5.39	4.96	8.47	5.73	(75)
25	1.49	1.51	1.54	1.56	1.58	1.60	1.62	1.63	1.64	1.65	1.65	1.62	(156)
26	1.53	1.53	1.55	1.60	1.70	1.90	2.25	2.84	3.78	5.27	7.71	9.04	(104)
27	3.36	3.34	3.30	3.24	3.17	3.10	3.14	3.49	4.60	7.17	12.76	5.55	(89)
28	1.97	2.02	2.06	2.10	2.14	2.18	2.20	2.22	2.23	2.23	2.23	2.29	(115)
29	3.70	3.72	3.72	3.69	3.61	3.47	3.22	2.82	2.29	1.93	3.41	2.19	(94)
30	2.78	2.84	2.89	2.95	3.00	3.06	3.11	3.16	3.21	3.26	3.30	3.19	(169)
31	5.35	5.41	5.44	5.44	5.38	5.25	5.00	4.56	3.86	2.92	3.19	2.67	(96)
32	1.03	1.05	1.08	1.11	1.14	1.17	1.20	1.24	1.28	1.32	1.36	2.05	(212)
33	1.30	1.21	1.10	1.00	0.99	1.25	2.00	3.42	6.03	11.39	27.06	4.04	(72)

Table IV (continued). **Variation of SE for different values of S_∞, using all valid points.** (Cases 18 - 33)

Cases 27 - 33 give more equivocal results. Nos. 27,29, 31 and 33 all fail to show the progressive rise of SE with increasing values for S_∞ . Values for SE in cases 29 and 31 behave as described above for cases 19 and 24. Values for SE in cases 27 and 33 show no initial rise, the SE first falling to a minimum and then rising again. As above, the implication here is that for all these cases the "ideal" value for S_∞ lies above 0 and that the use of "excess" sugar is to be preferred. Cases 29 and 31 show the SE when $S_\infty = S_f$ to be less than when $S_\infty = 0$ but only in case 31 is SE <u>minimal</u> when $S_\infty = S_f$. In the other three cases minimum SE is obtained at a value for S_∞ less than S_f.

Table V shows, as above, the variation of SE from best-fitting straight lines through series of points obtained in each case by allocating the same arbitrary values to S_∞ as described for Table IV. This time, however, blood glucose readings prior to the 20th minute after glucose injection have been omitted from the calculations. In this way any distortion of the blood glucose slope which might have been produced by the relatively rapid blood glucose fall in the early minutes of the IVGTT has largely been eliminated. It will be seen that the SE of points from best-fitting straight lines is less in nearly all cases and for nearly all values of S_∞ than corresponding figures in Table IV. This confirms the view that in general the middle section of an IVGTT blood glucose slope is more nearly a straight line than the slope taken as a whole.

Case No.	$S_\infty = 0$	$S_\infty = +10$	$S_\infty = +20$	$S_\infty = +30$	$S_\infty = +40$	$S_\infty = +50$	$S_\infty = +60$	$S_\infty = +70$	$S_\infty = +80$	$S_\infty = +90$	$S_\infty = +100$	$S_\infty = S_f$	(S_f)
1	2.84	2.95	3.06	3.19	3.32	3.47	3.63	3.81	4.00	4.22	4.45	5.08	(122)
2	1.44	1.52	1.61	1.71	1.83	1.97	2.15	2.36	2.63	3.00	3.52	3.52	(100)
3	1.03	1.07	1.11	1.15	1.21	1.26	1.33	1.41	1.51	1.64	1.82	1.82	(100)
4	0.31	0.33	0.35	0.37	0.40	0.43	0.46	0.50	0.54	0.59	0.64	10.59	(263)
5	1.78	1.85	1.94	2.02	2.12	2.23	2.29	2.47	2.62	2.78	2.96	8.05	(200)
6	2.12	2.24	2.39	2.55	2.74	2.96	3.22	3.53	3.91	4.37	4.96	4.59	(94)
7	1.23	1.29	1.36	1.44	1.53	1.63	1.74	1.88	2.04	2.23	2.46	2.62	(106)
8	1.01	1.06	1.11	1.17	1.24	1.32	1.41	1.51	1.64	1.78	1.96	2.42	(119)
9	1.58	1.66	1.75	1.86	1.98	2.11	2.27	2.44	2.65	2.89	3.18	2.83	(88)
10	2.33	2.40	2.47	2.54	2.62	2.71	2.79	2.89	2.99	3.09	3.21	4.25	(171)
11	1.23	1.26	1.30	1.35	1.39	1.44	1.49	1.54	1.60	1.66	1.73	5.42	(260)
12	1.14	1.18	1.21	1.25	1.29	1.33	1.38	1.43	1.48	1.53	1.59	2.16	(192)
13	4.05	4.45	4.94	5.54	6.29	7.26	8.54	10.30	12.87	16.95	24.34	16.10	(88)
14	1.51	1.58	1.65	1.72	1.80	1.88	1.98	2.11	2.31	2.73	3.82	3.02	(94)
15	3.38	3.49	3.60	3.71	3.84	3.97	4.12	4.28	4.45	4.63	4.84	4.95	(105)
16	2.52	2.69	2.88	3.11	3.40	3.76	4.23	4.89	5.83	7.33	10.00	6.49	(85)
17	3.80	4.00	4.22	4.46	4.74	5.05	5.40	5.81	6.28	6.83	7.48	6.38	(82)

Table V. Variation of SE for different values of S_∞, omitting the first three valid points. (Cases 1 - 17)

Case No.	$S_\infty = 0$	$S_\infty = +10$	$S_\infty = +20$	$S_\infty = +30$	$S_\infty = +40$	$S_\infty = +50$	$S_\infty = +60$	$S_\infty = +70$	$S_\infty = +80$	$S_\infty = +90$	$S_\infty = +100$	$S_\infty = S_f$	(S_f)
18	1.41	1.49	1.58	1.70	1.86	2.08	2.39	2.87	3.64	4.94	7.34	3.74	(81)
19	1.41	1.49	1.58	1.70	1.86	2.08	2.39	2.87	3.64	4.94	7.34	4.54	(88)
20	7.44	8.00	8.65	9.42	10.35	11.50	12.95	14.85	17.47	21.37	27.93	19.20	(85)
21	3.88	4.21	4.60	5.08	5.67	6.44	7.46	8.91	11.11	14.88	22.86	12.57	(85)
22	1.81	1.87	1.92	1.98	2.04	2.10	2.17	2.24	2.31	2.39	2.47	2.58	(113)
23	2.00	2.12	2.25	2.39	2.56	2.76	2.99	3.27	3.61	4.04	4.60	2.99	(60)
24	2.38	2.52	2.67	2.83	3.03	3.25	3.53	3.90	4.48	5.73	9.66	4.15	(75)
25	0.53	0.55	0.56	0.57	0.58	0.60	0.61	0.63	0.65	0.68	0.71	1.34	(156)
26	1.04	1.19	1.36	1.58	1.86	2.21	2.69	3.33	4.24	5.61	7.79	8.99	(104)
27	0.83	1.01	1.13	1.29	1.49	1.79	2.21	2.87	3.93	5.85	9.89	5.77	(89)
28	0.53	0.54	0.56	0.61	0.67	0.75	0.84	0.96	1.13	1.32	1.60	2.25	(115)
29	1.03	0.76	0.75	0.73	0.69	0.61	0.49	0.34	0.43	1.15	2.76	1.65	(94)
30	1.39	1.48	1.52	1.58	1.63	1.69	1.75	1.81	1.89	1.96	2.05	2.92	(169)
31	1.52	1.06	1.04	1.01	0.94	0.84	0.67	0.48	0.63	1.57	3.68	2.57	(96)
32	0.32	0.36	0.37	0.38	0.39	0.40	0.42	0.43	0.45	0.47	0.48	0.89	(212)
33	0.70	0.73	0.78	0.90	1.11	1.49	2.16	3.32	5.52	10.30	25.68	3.66	(72)

Table V (continued). **Variation of SE for different values of S_∞, omitting the first three valid points.** (Cases 18 - 33)

It will also be seen that in all cases minimum SE is obtained when $S_\infty = 0$ and that an increase in the value of S_∞ results in a progressive rise of SE. This confirms that the use of "total" blood glucose is preferable to that of "excess" blood glucose in the calculation of k in an IVGTT.

Results for cases 27 - 33 in general support this conclusion. Nos. 29 and 31 show a fall followed by a rise of SE for increasing values of S_∞ but in both cases minimum SE is obtained when S_∞ is substantially less than S_f.

Section of Slope to be used

Table VI shows the effect produced on the k values in each case by omission of the earlier points of the IVGTT blood glucose/time graph. For this purpose S_∞ is taken as zero. The first and second column of this table record respectively the case number and the maximum number (referred to as "X") of valid blood glucose points for each test. The remaining columns show the values of k calculated from best-fitting straight lines obtained first by using all valid points (points "1-X"), then by using all points except the first ("2-X"), then all except the first two ("3-X") and so on until only the last four or five points are used. For each combination of points in each case the SE of the observed points from best-fitting straight lines has also been calculated and is shown in brackets below the various k values.

Case No.	Valid points (X)	k and SE (in brackets) for points :- 1 to X	2 to X	3 to X	4 to X	5 to X	6 to X	7 to X
1	11	0.85 (4.39)	0.77 (3.65)	0.71 (3.56)	0.62 (2.84)	0.54 (2.47)	0.41 (0.66)	0.40 (0.69)
2	11	0.86 (2.26)	0.83 (2.26)	0.80 (2.09)	0.73 (1.44)	0.69 (1.13)	0.72 (1.07)	0.76 (1.02)
3	11	0.91 (1.10)	0.89 (0.92)	0.90 (0.96)	0.90 (1.03)	0.90 (1.12)	0.89 (1.23)	0.86 (1.34)
4	10	0.86 (3.07)	0.75 (0.46)	0.76 (0.38)	0.77 (0.31)	0.79 (0.24)	0.80 (0.17)	0.82 (0.12)
5	11	0.77 (2.52)	0.81 (2.33)	0.85 (2.08)	0.90 (1.78)	0.96 (1.40)	1.02 (1.01)	1.06 (0.92)
6	11	1.17 (3.33)	1.12 (3.04)	1.05 (2.59)	0.99 (2.12)	1.05 (1.64)	1.11 (1.40)	1.11 (1.62)
7	11	0.83 (1.92)	0.82 (1.96)	0.79 (1.90)	0.73 (1.23)	0.73 (1.34)	0.75 (1.45)	0.83 (0.77)
8	11	0.91 (4.58)	0.80 (2.92)	0.70 (1.22)	0.74 (1.01)	0.76 (0.88)	0.77 (0.95)	0.74 (0.86)
9	11	0.63 (1.70)	0.64 (1.79)	0.67 (1.69)	0.70 (1.58)	0.74 (1.43)	0.79 (1.29)	0.83 (1.23)
10	11	0.86 (4.43)	0.75 (2.70)	0.71 (2.66)	0.65 (2.33)	0.55 (0.66)	0.51 (0.16)	0.52 (0.12)
11	11	0.42 (1.19)	0.43 (1.24)	0.45 (1.21)	0.46 (1.23)	0.47 (1.33)	0.48 (1.45)	0.50 (1.50)
12	11	0.64 (1.66)	0.62 (1.58)	0.60 (1.58)	0.55 (1.14)	0.51 (0.71)	0.50 (0.76)	0.48 (0.79)
13	10	1.81 (6.15)	1.61 (3.55)	1.65 (3.69)	1.65 (4.05)	1.77 (4.05)	1.93 (4.08)	2.18 (4.15)
14	10	1.34 (1.79)	1.39 (1.31)	1.40 (1.38)	1.40 (1.51)	1.38 (1.65)	1.32 (1.71)	1.19 (1.51)
15	11	1.05 (3.84)	0.99 (3.35)	0.98 (3.56)	0.91 (3.38)	0.78 (2.04)	0.82 (2.14)	0.83 (2.45)
16	11	1.46 (2.89)	1.51 (2.44)	1.56 (2.33)	1.56 (2.52)	1.60 (2.58)	1.63 (2.80)	1.63 (3.23)
17	11	1.08 (3.66)	1.02 (3.40)	1.02 (3.63)	0.98 (3.80)	0.89 (3.56)	0.83 (3.77)	0.70 (3.66)

Table VI. Variation of k and SE for different sections of the blood glucose / blood sugar vs. time graphs. ($S_\infty = 0$) Cases 1 - 17.

Case No.	Valid points (X)	k and SE (in brackets) for points :- 1 to X	2 to X	3 to X	4 to X	5 to X	6 to X	7 to X
18	11	1.31 (1.69)	1.34 (1.51)	1.36 (1.41)	1.38 (1.41)	1.40 (1.51)	1.40 (1.69)	1.37 (1.90)
19	11	1.62 (4.30)	1.52 (2.91)	1.49 (2.97)	1.38 (1.41)	1.40 (1.51)	1.40 (1.69)	1.37 (1.90)
20	8	2.13 (6.55)	2.10 (7.16)	2.01 (7.85)	2.42 (7.44)	3.47 (3.09)	- -	- -
21	9	2.08 (5.38)	2.01 (5.63)	1.76 (3.73)	1.86 (3.88)	1.79 (4.37)	1.99 (4.87)	- -
22	11	1.03 (2.11)	0.98 (1.61)	0.99 (1.71)	0.98 (1.81)	0.98 (1.99)	0.89 (1.23)	0.86 (1.34)
23	11	0.91 (2.75)	0.86 (2.13)	0.82 (1.91)	0.83 (2.00)	0.83 (2.19)	0.85 (2.42)	0.82 (2.74)
24	10	2.08 (6.31)	1.94 (5.49)	1.76 (3.97)	1.58 (2.38)	1.61 (2.60)	1.44 (1.83)	1.31 (1.63)
25	11	0.76 (1.49)	0.72 (0.78)	0.71 (0.62)	0.69 (0.53)	0.68 (0.51)	0.67 (0.55)	0.68 (0.61)
26	10	1.65 (1.53)	1.61 (1.04)	1.58 (0.98)	1.57 (1.04)	1.61 (0.91)	1.66 (0.84)	1.75 (0.31)
27	9	1.72 (3.36)	1.61 (1.84)	1.52 (0.83)	1.53 (0.92)	1.53 (1.06)	1.56 (1.27)	- -
28	8	0.78 (1.97)	0.73 (0.97)	0.69 (0.53)	0.67 (0.48)	0.67 (0.58)	- -	- -
29	7	1.51 (3.70)	1.38 (1.83)	1.29 (1.03)	1.24 (0.76)	- -	- -	- -
30	9	0.80 (2.78)	0.72 (1.45)	0.70 (1.39)	0.69 (1.43)	0.66 (1.50)	0.63 (1.59)	- -
31	8	1.69 (5.35)	1.51 (3.39)	1.38 (1.52)	1.33 (1.06)	1.28 (0.77)	- -	- -
32	11	0.37 (1.03)	0.34 (0.49)	0.32 (0.32)	0.32 (0.35)	0.32 (0.38)	0.31 (0.34)	0.28 (0.21)
33	11	1.53 (1.30)	1.51 (1.19)	1.48 (1.00)	1.45 (0.70)	1.43 (0.69)	1.41 (0.67)	1.42 (0.76)

Table VI (continued). Variation of k and SE for different sections of the blood glucose / blood sugar vs. time graphs. ($S_\infty = 0$) Cases 18 - 33.

It will be seen that in the majority of cases values for k decrease if the first point is omitted. Values usually fall by rather less if the second point is also omitted and omission of further points results either in a progressive fall in k value (for example, Nos. 1, 12 and 17) or a fall followed by a rise (for example, Nos. 2, 7 and 26). In four cases (Nos. 5, 9, 11 and 16) there is a steady rise.

There is no essential difference between the results obtained here for cases 1 - 26 and those obtained for cases 27 - 33.

It is commonly assumed that a good straight line or exponential relationship between blood glucose (or blood sugar) and time is not established until at least 20 minutes after glucose injection. Using the present technique, the 20 minute blood glucose/blood sugar reading is the fourth point on the graph (or the third point for Cases 27-33,) and the supposed true exponential section of the slope would be represented in Table VI, therefore, by k values in column "4-X" (or "3-X" for Cases 27 - 33).

It has already been explained that because of the scatter of points in an actual IVGTT omission of any point will almost certainly affect the k value calculated from the remainder. This variation of k makes it impossible to be categorical as to the limits of the true exponential section of the blood glucose/blood sugar slope. In such circumstances it might be thought that calculation of the SE for each section of the slope would provide a further clue - the smaller the SE of a series of points from a best-fitting straight line

the closer those points approximate to the line. Unfortunately this is of little help. The SE from best-fitting straight lines of points lying in a curve will vary according to the arc of curve considered, the SE being smaller the smaller the arc, irrespective of the number of points involved. Similar considerations will also apply to a scattered series of points such as an actual IVGTT graph. It is no surprise, therefore, to find that in the range considered here no less than 17 cases out of 33 have a minimum SE when a short section only (that is, the last four or five points) of the slope is taken. This may indicate that no true straight line section exists in an IVGTT blood glucose/blood sugar slope, although on the other hand it may merely reflect the scatter of points. Inspection of Table VI and Figures V to XXXVII indicates, however, that in most cases deviation from best-fitting straight lines is small. While no particular section of the curve is always clearly superior to other sections, that part from the "twenty minute" point onwards usually represents the slope fairly well. In Figures V to XXXVII best-fitting lines calculated from this section of each curve have been drawn.

In these Figures individual IVGTT's are shown, blood glucose - or, for Cases 27 - 33, blood sugar - (in mg per ml) being plotted against time after glucose injection (in minutes) on semilogarithmic graph paper. On each Figure two series of points have been plotted to represent "total" blood glucose ($S_{\infty} = 0$) and "excess" blood glucose ($S_{\infty} = S_f$) and blood glucose values less than 25 mg per

100 ml in excess of S_f have been omitted. For each series of points best-fitting straight lines (based on points "4-X" for Cases 1 - 26 and on points "3-X" for Cases 27 - 33), calculated mathematically, have been annotated with their respective values of k and the SE from the points they represent.

Once again there is no essential difference between the graphs of individual IVGTT's in cases 1 - 24 and either the mean values for the diabetics and non-diabetics in this series (cases 25 and 26) or other series (cases 27 - 33).

It is interesting to note that although in most cases the first two or three points deviate significantly from a straight line fitted to the remainder, they approximate fairly closely to it in several tests (if "total" blood glucose is used) - for example, Nos. 3, 9, 11, 14 and 18. This indicates that on occasion, at least, a good straight line or simple exponential relationship appears to exist between blood glucose and time almost from the very start of an IVGTT.

As seen already from Table V these graphs show that in almost every case use of "total" blood glucose/blood sugar in the calculation provides a better straight line fit than use of "excess" blood glucose/ blood sugar.

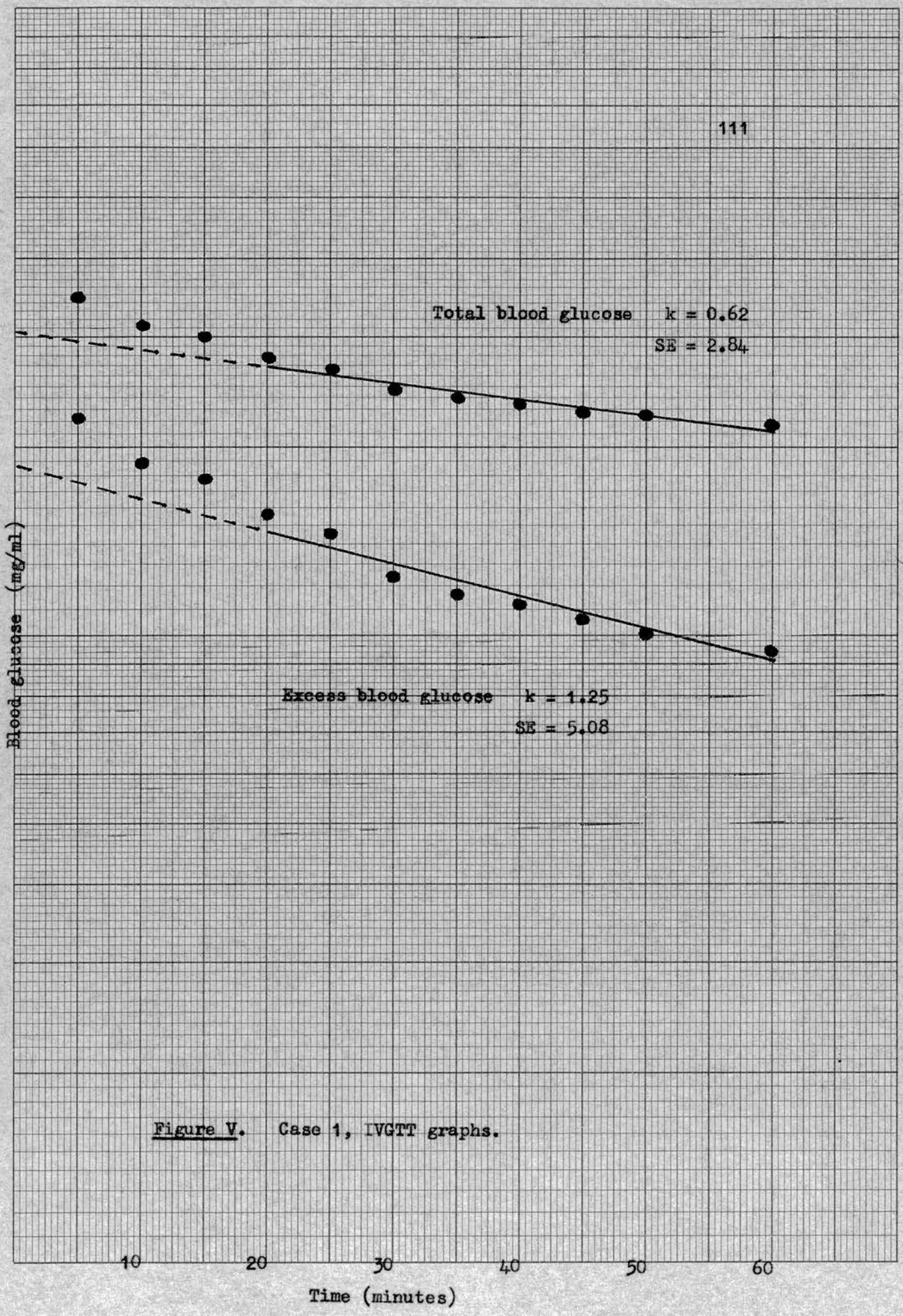

Figure V. Case 1, IVGTT graphs.

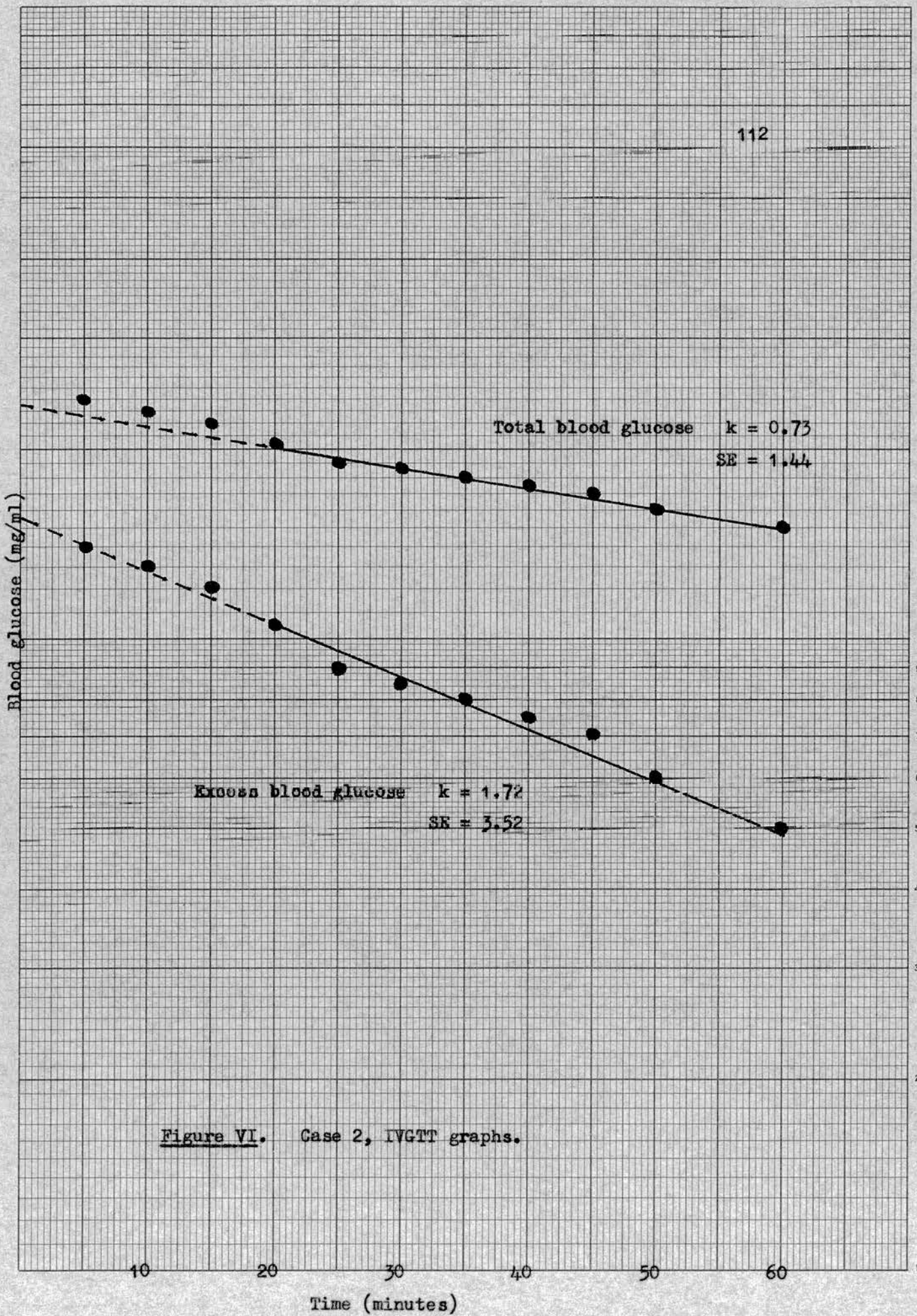

Figure VI. Case 2, IVGTT graphs.

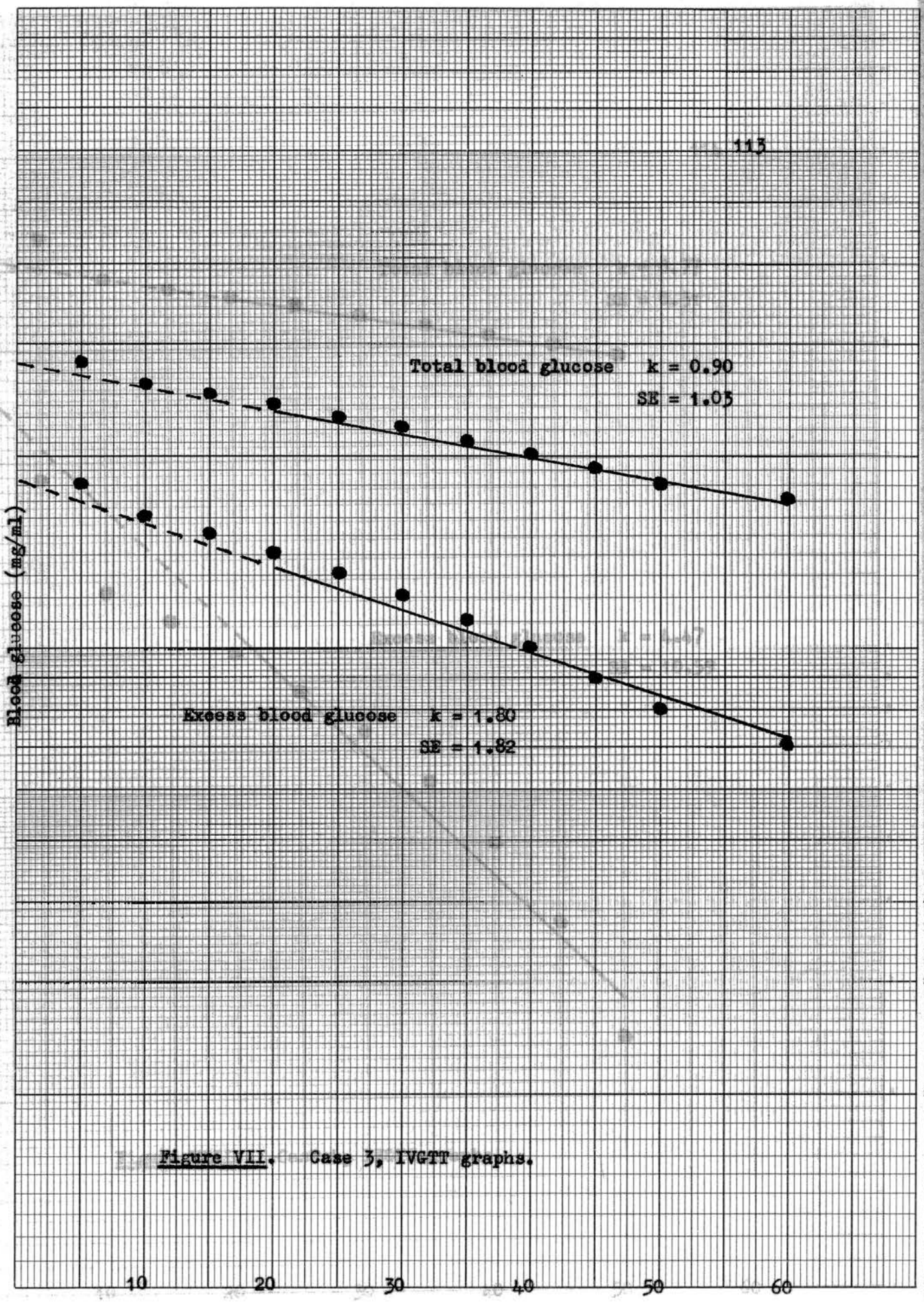

Figure VII. Case 3, IVGTT graphs.

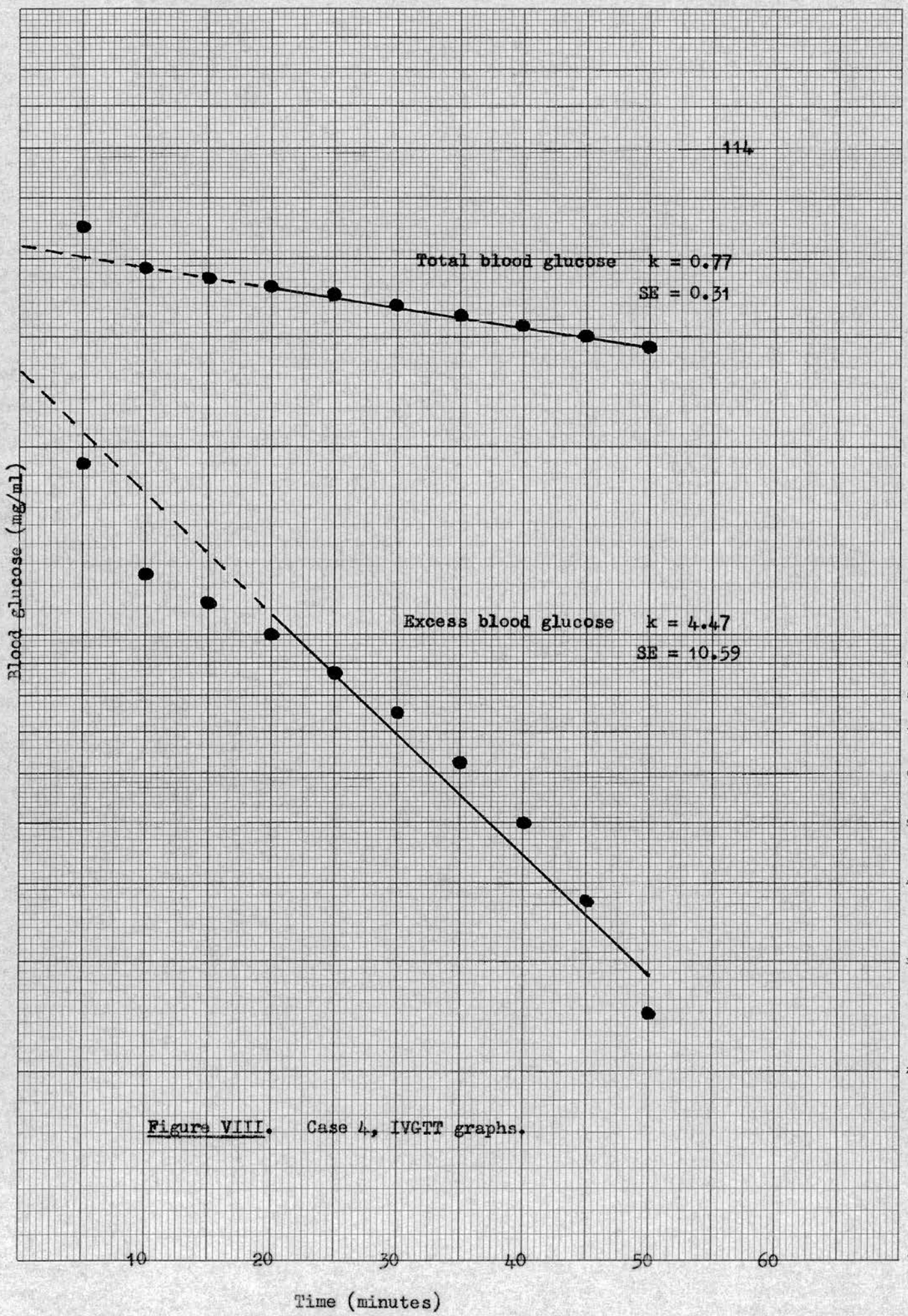

Figure VIII. Case 4, IVGTT graphs.

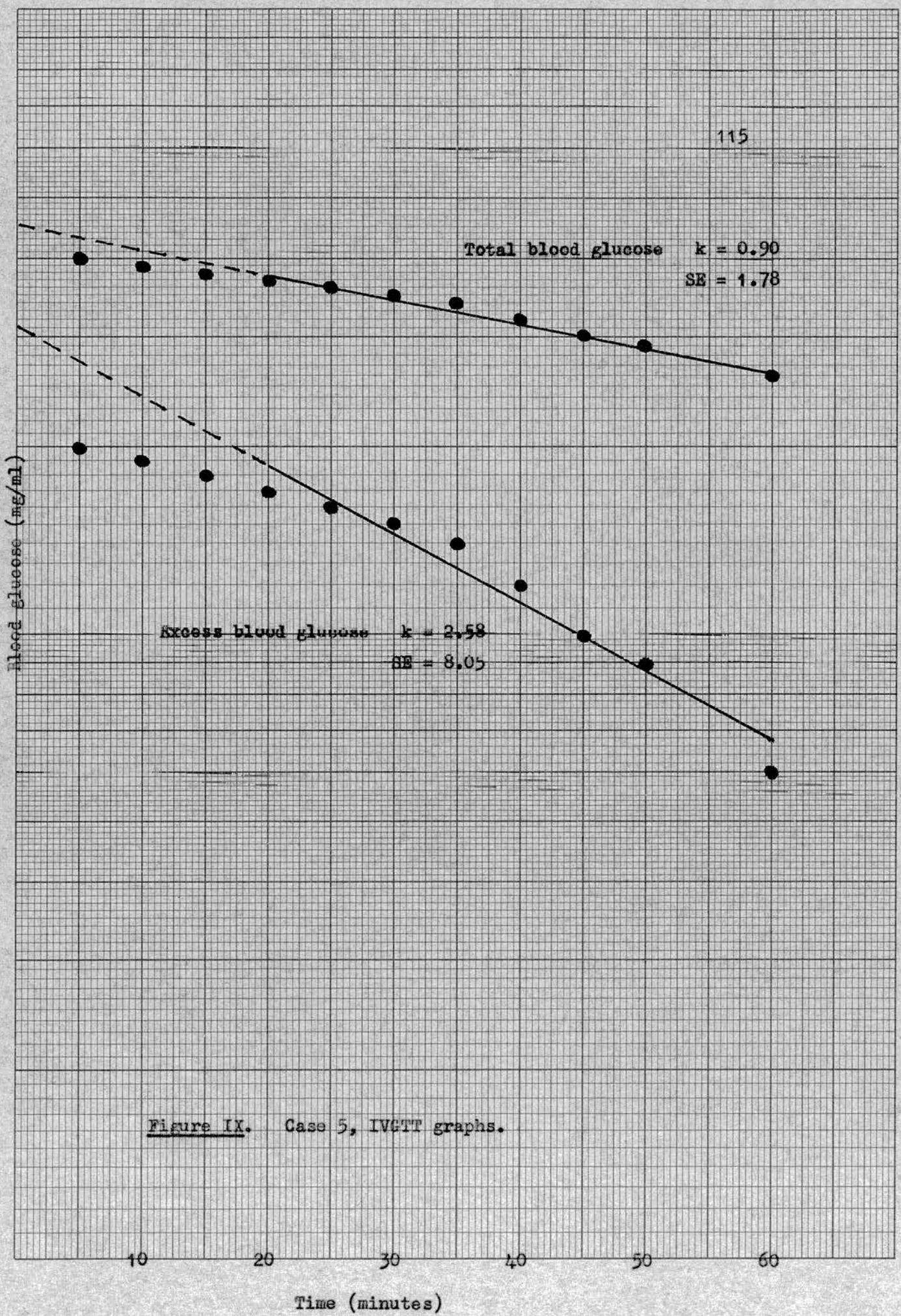

Figure IX. Case 5, IVGTT graphs.

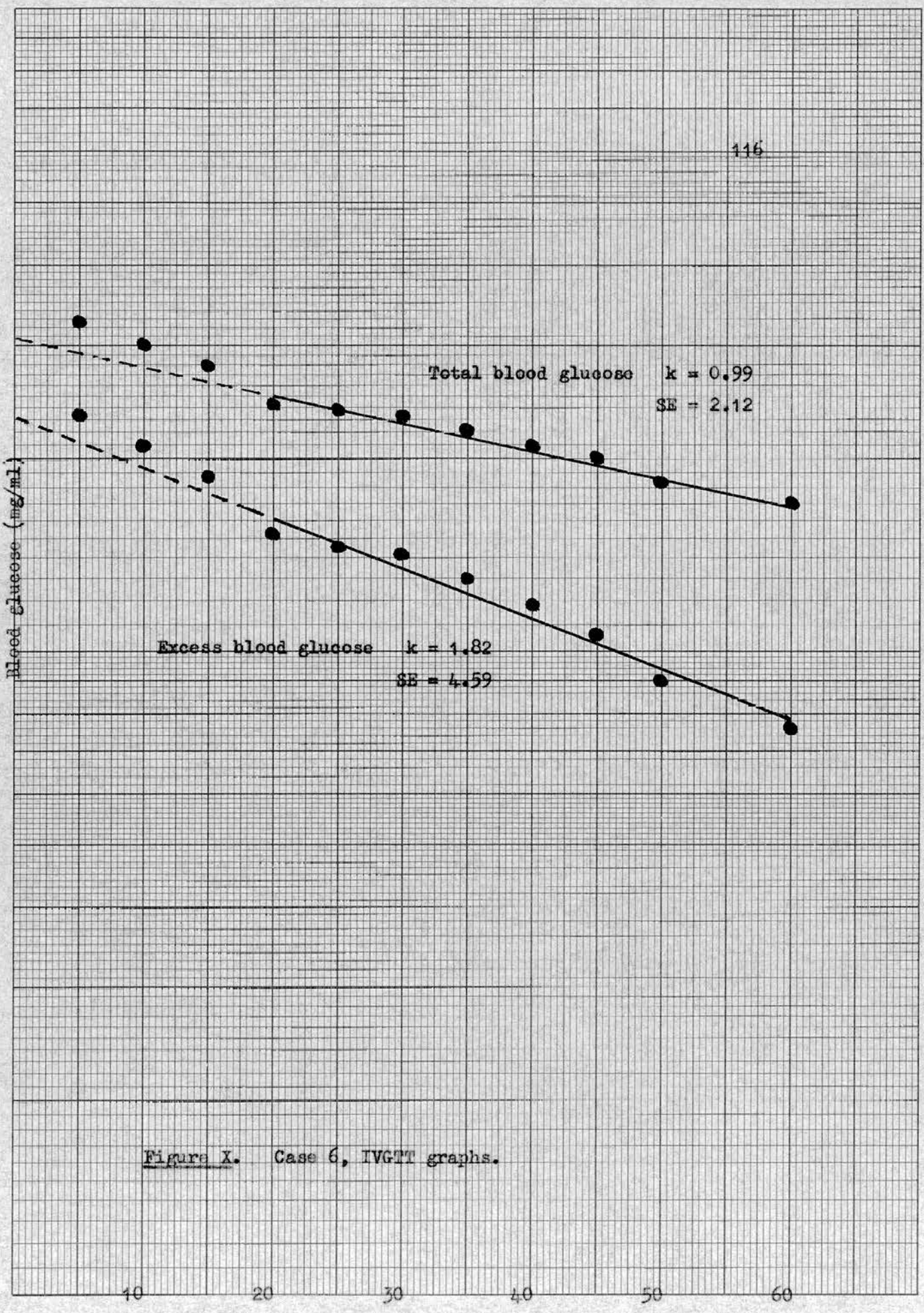

Figure X. Case 6, IVGTT graphs.

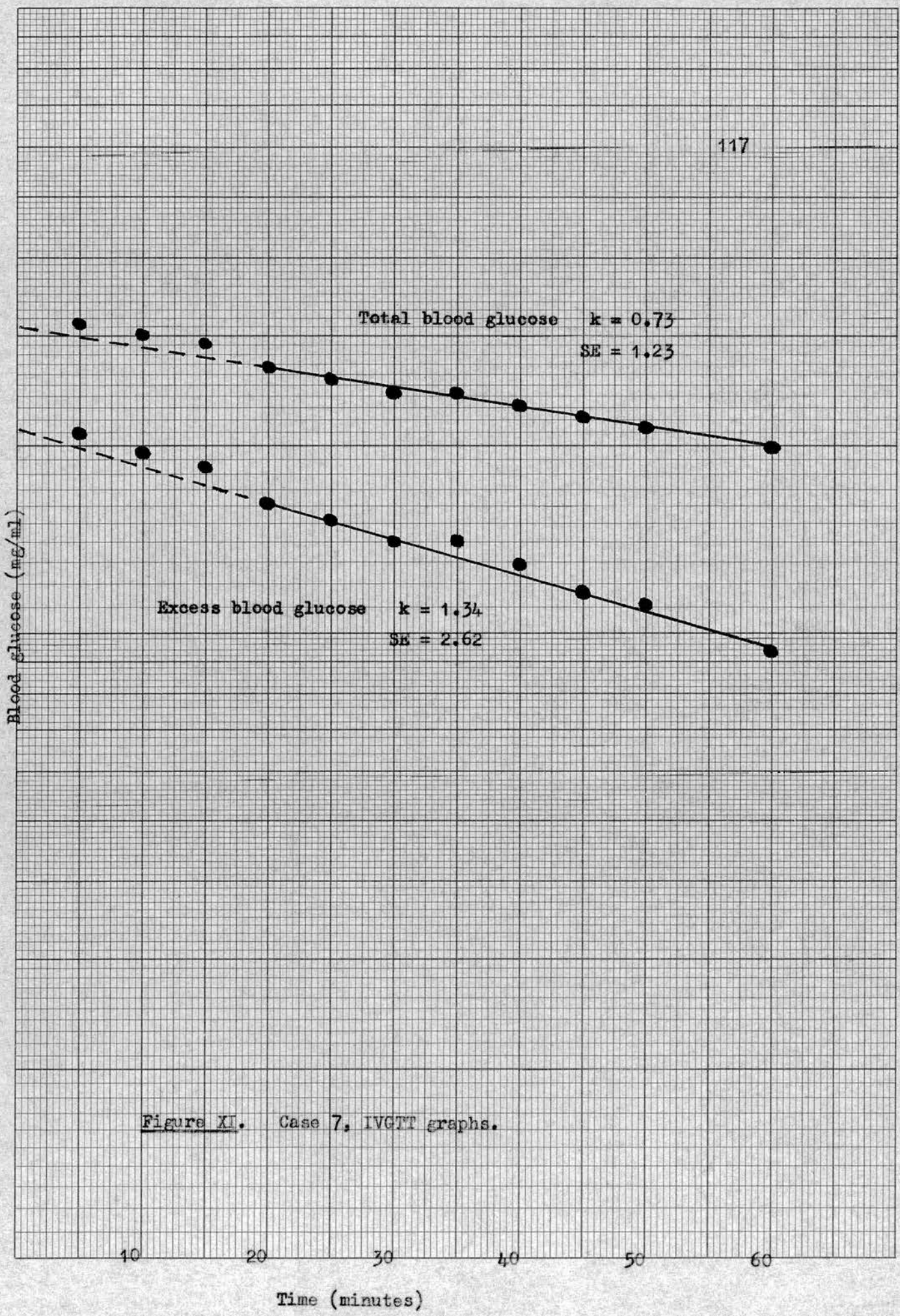

Figure XI. Case 7. IVGTT graphs.

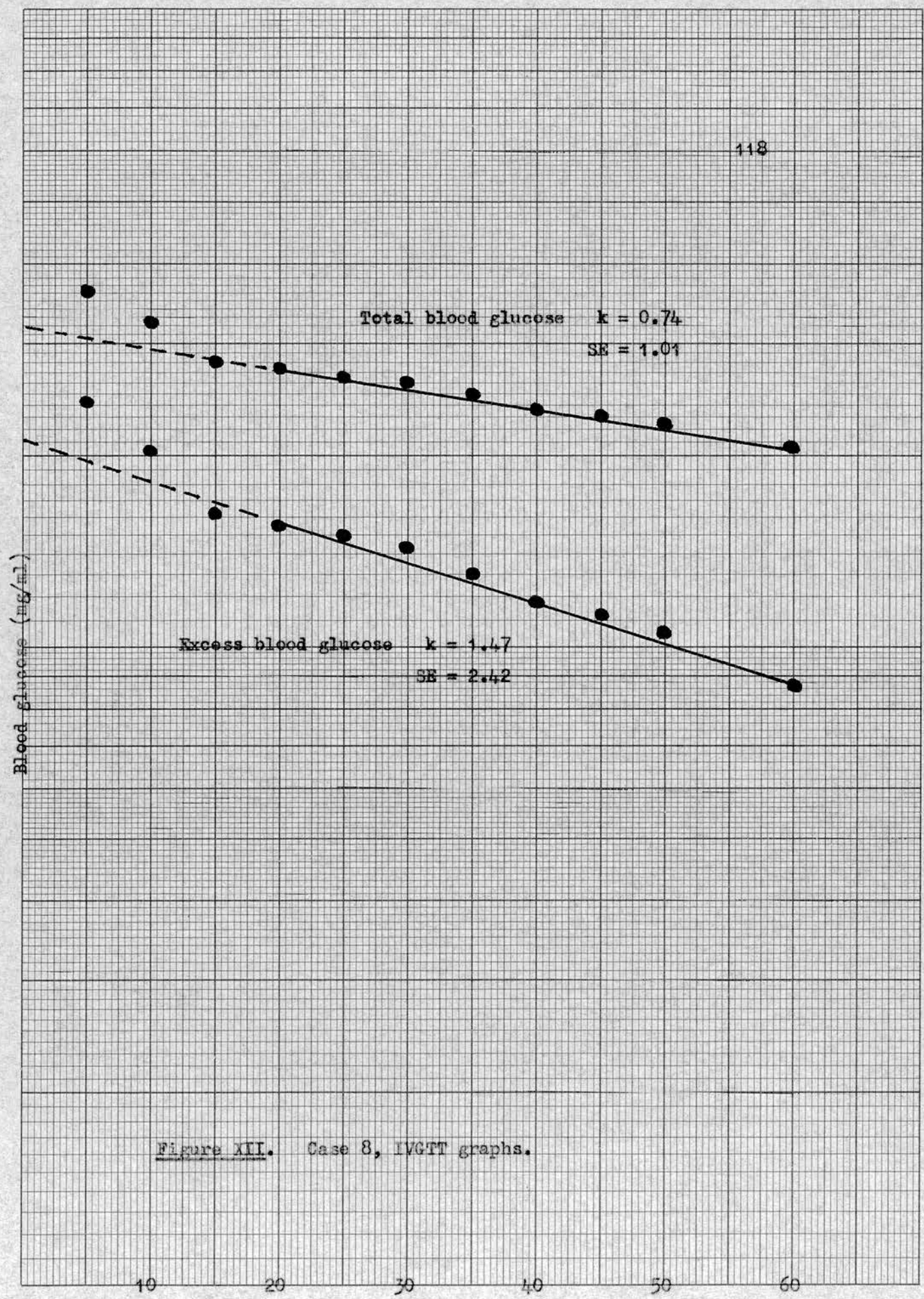

Figure XII. Case 8, IVGTT graphs.

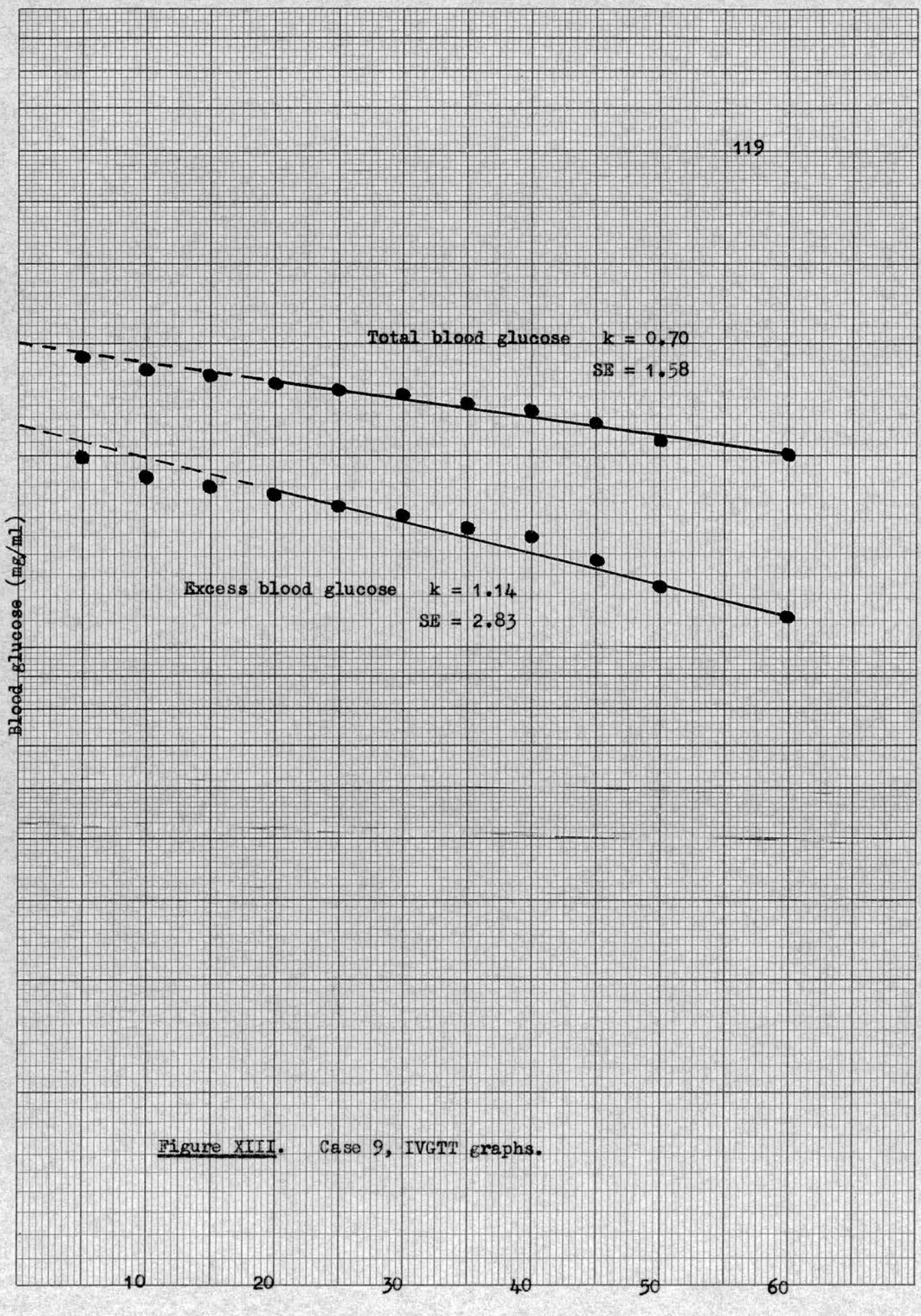

Figure XIII. Case 9, IVGTT graphs.

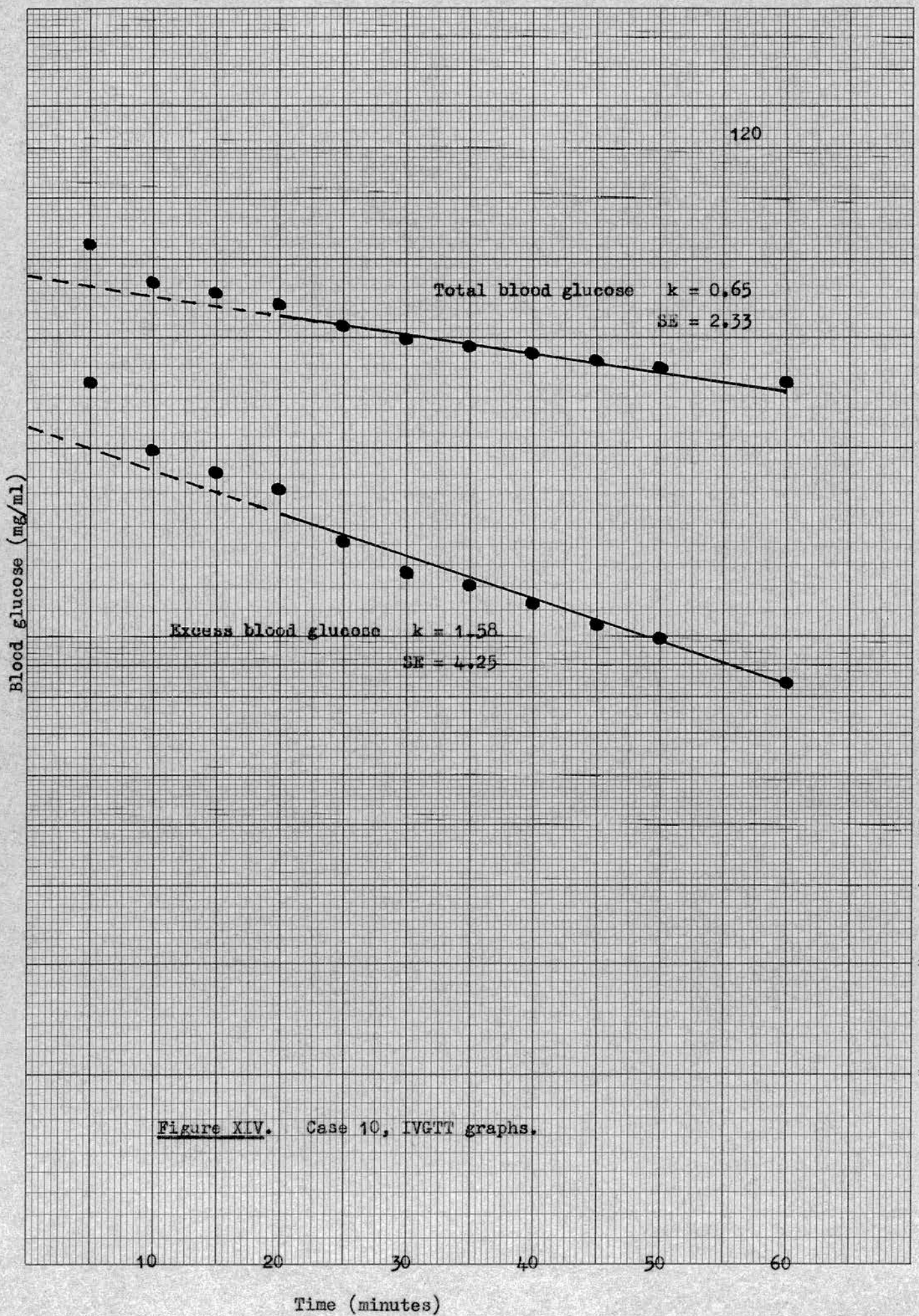

Figure XIV. Case 10, IVGTT graphs.

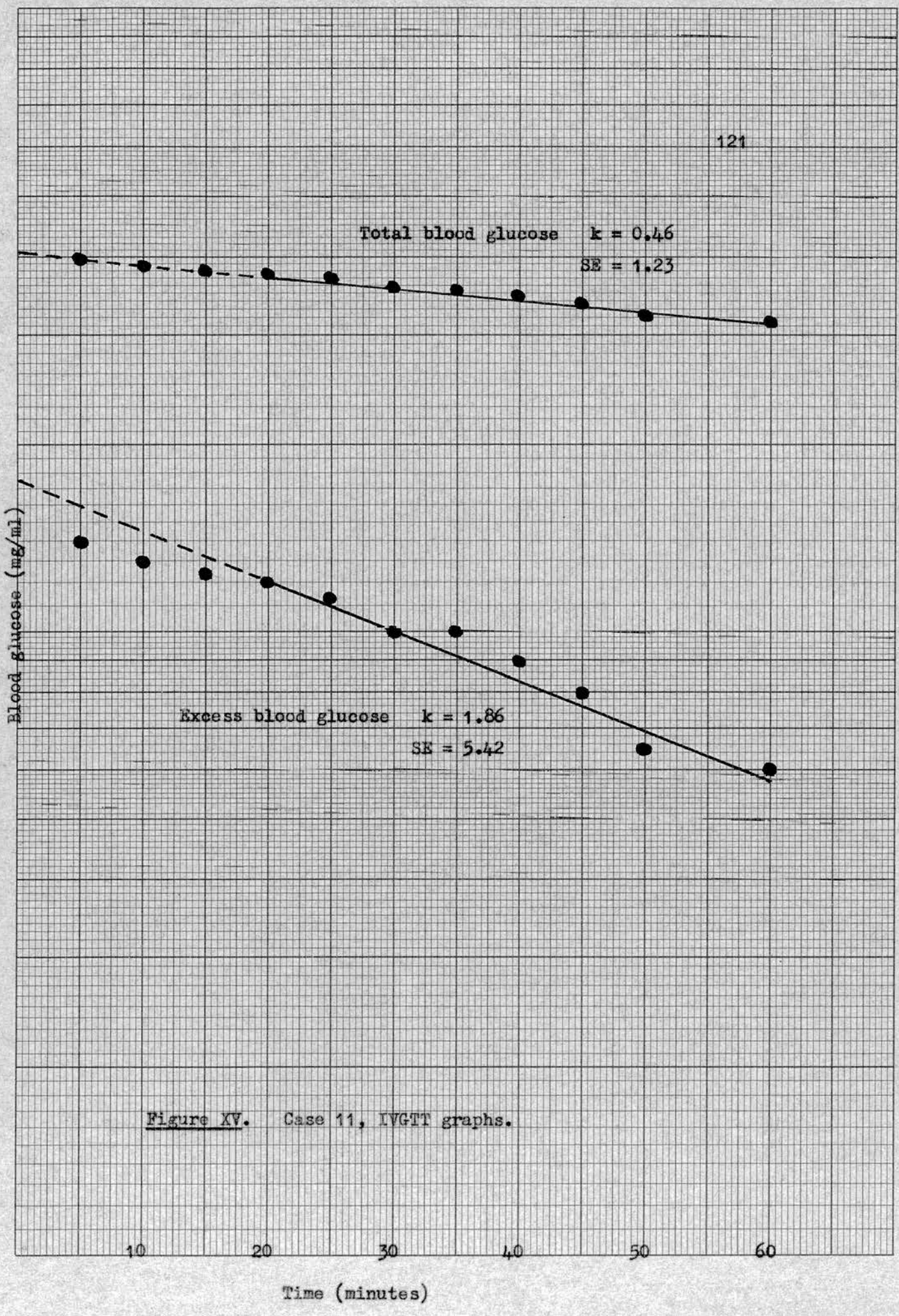

Figure XV. Case 11, IVGTT graphs.

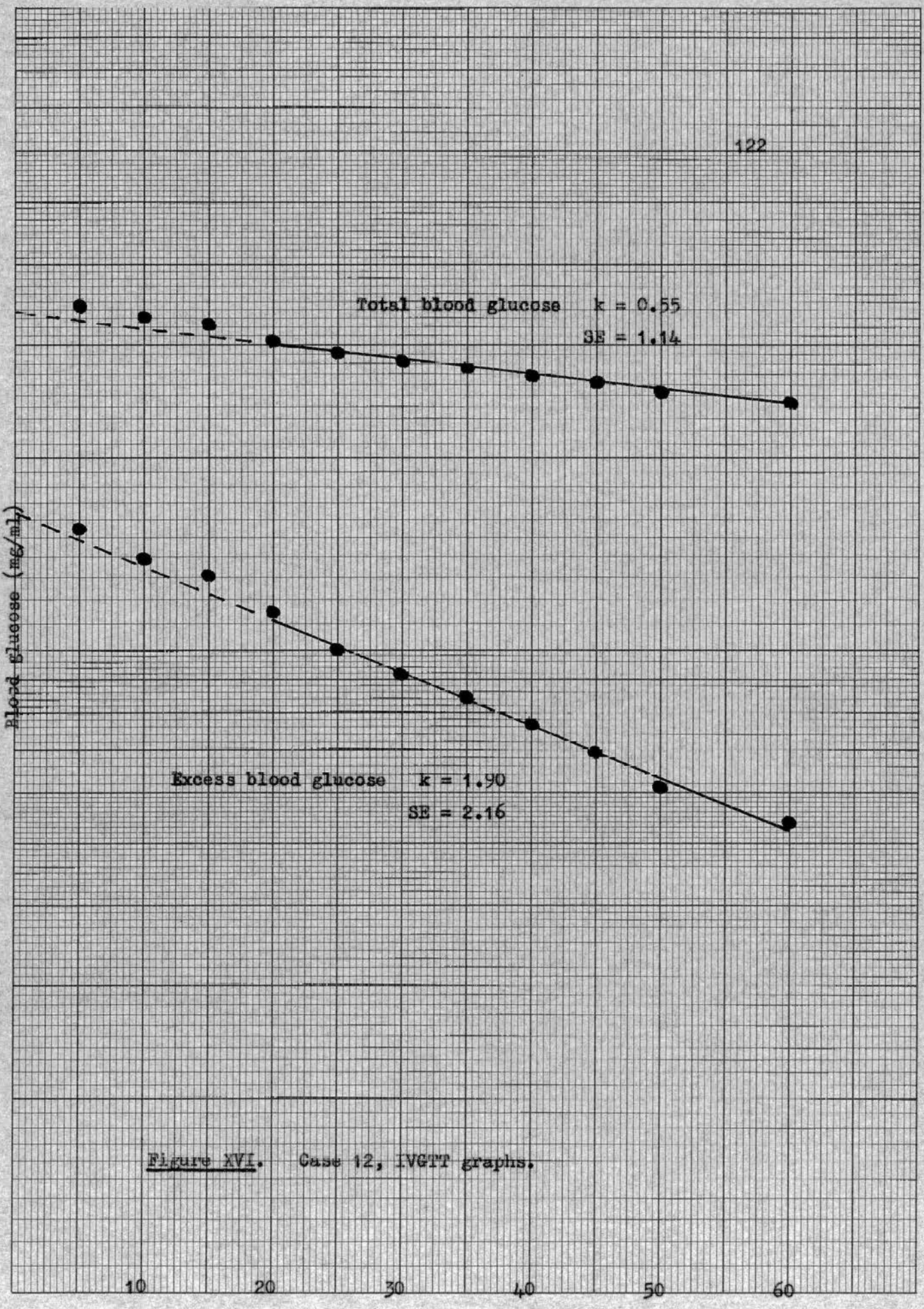

Figure XVI. Case 12, IVGTT graphs.

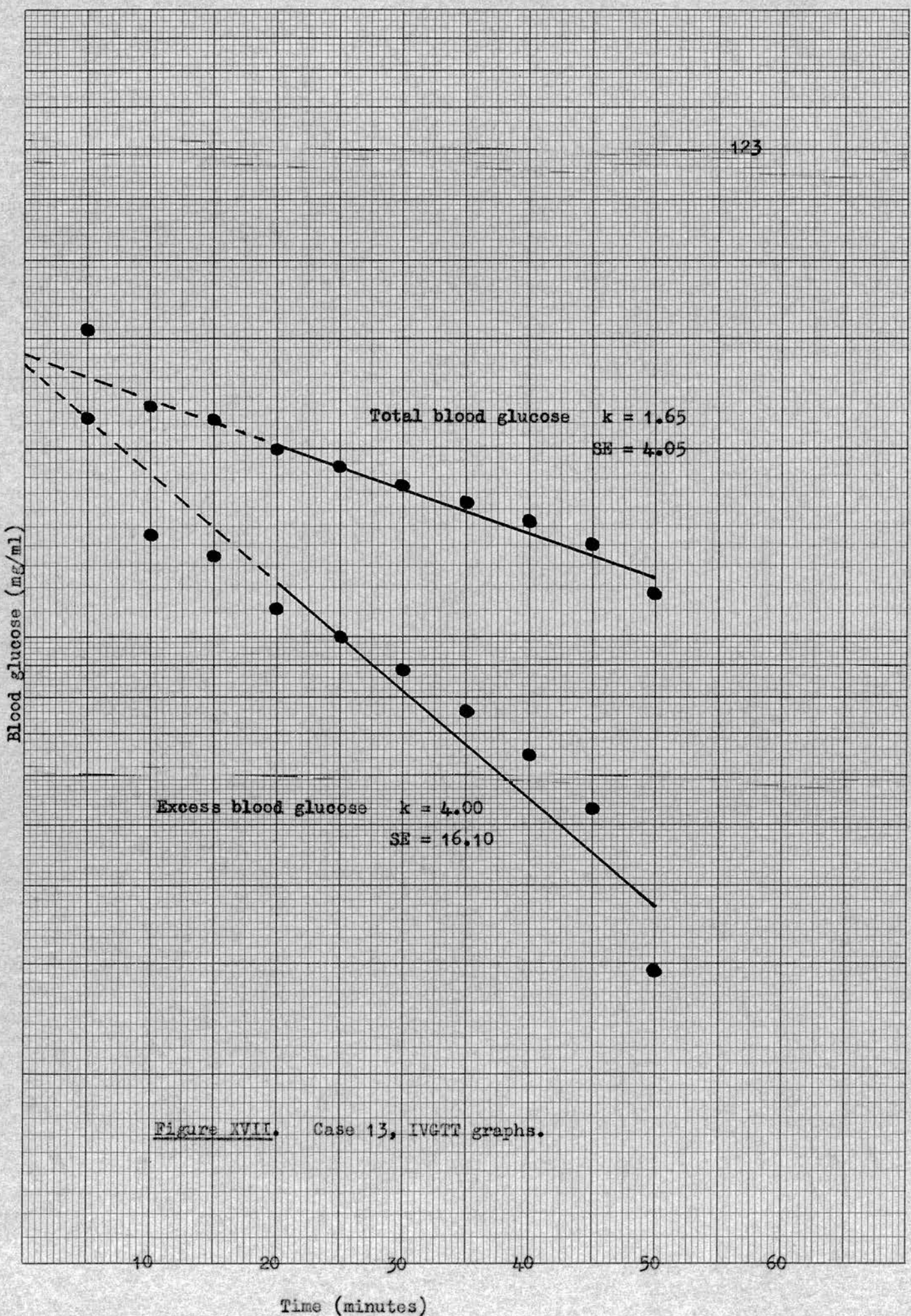

Figure XVII. Case 13, IVGTT graphs.

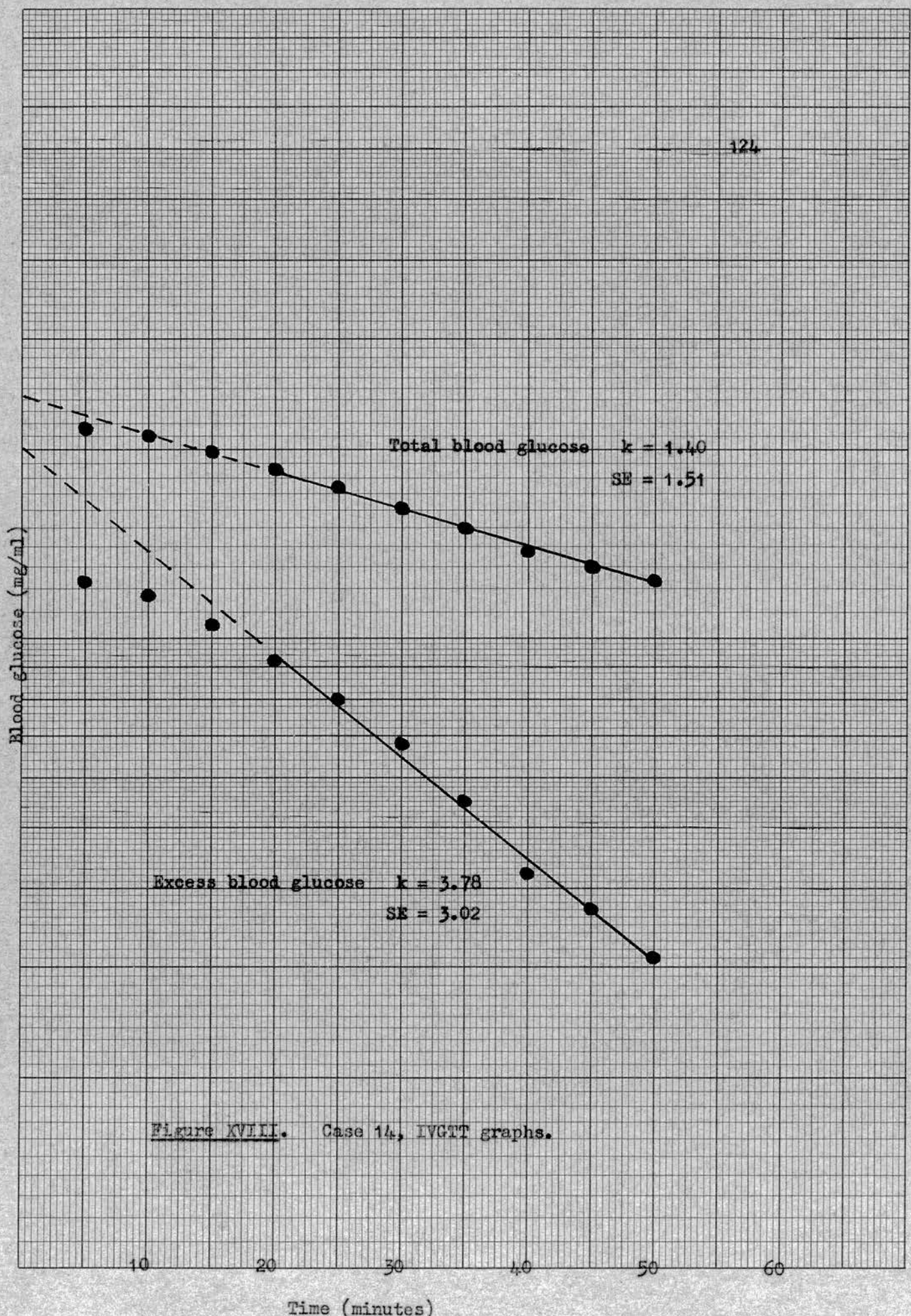

Figure XVIII. Case 14, IVGTT graphs.

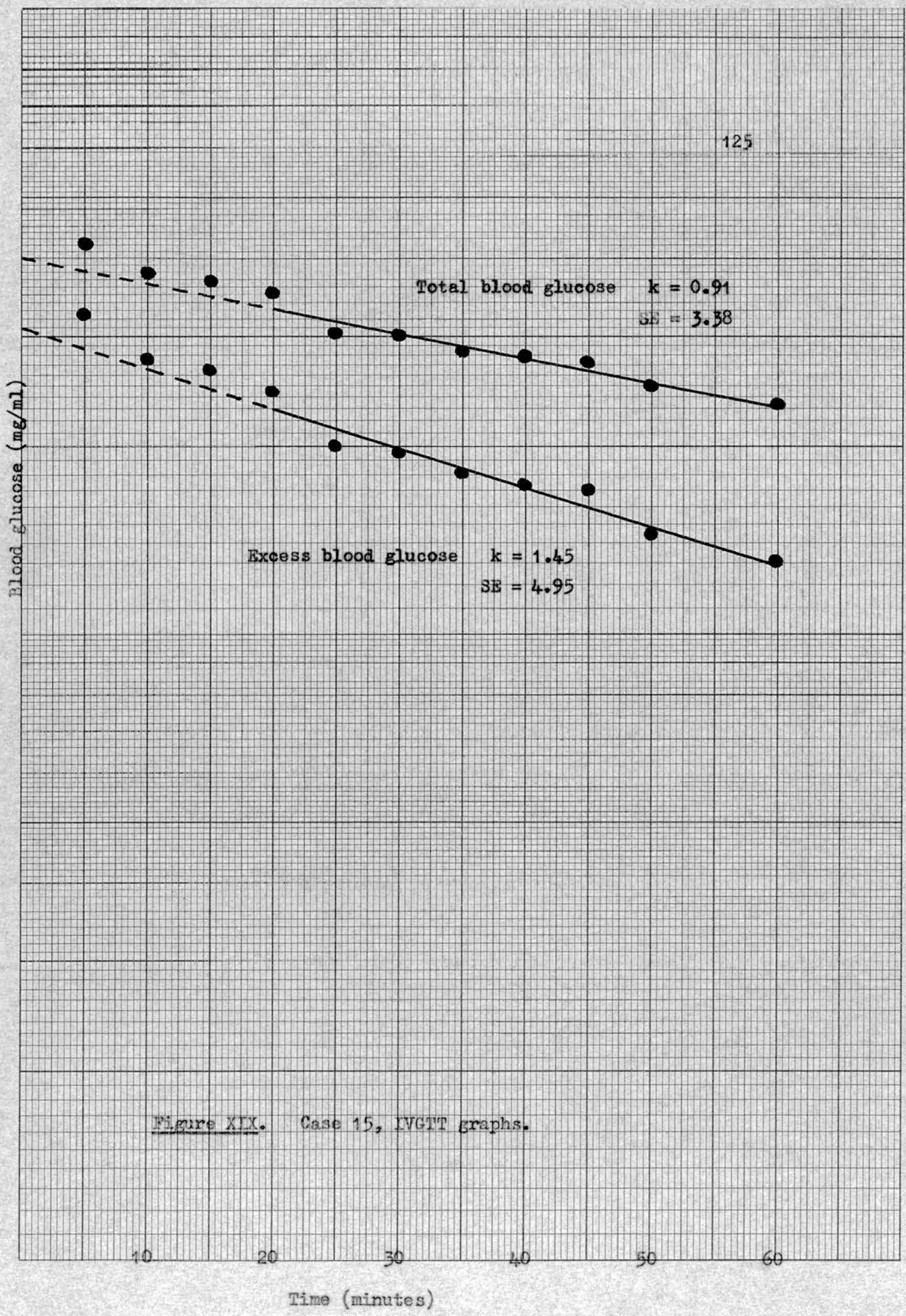

Figure XIX. Case 15, IVGTT graphs.

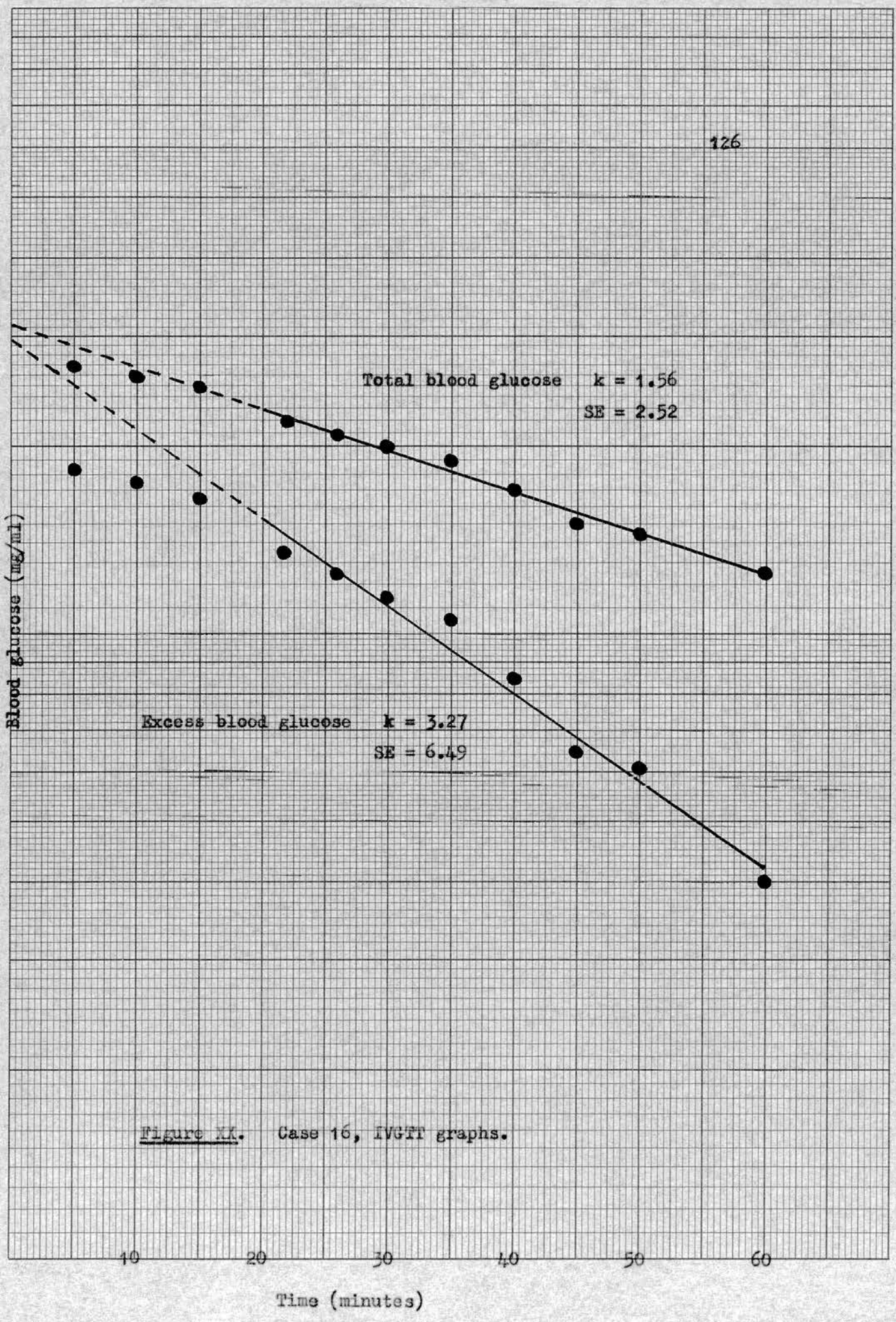

Figure XX. Case 16, IVGTT graphs.

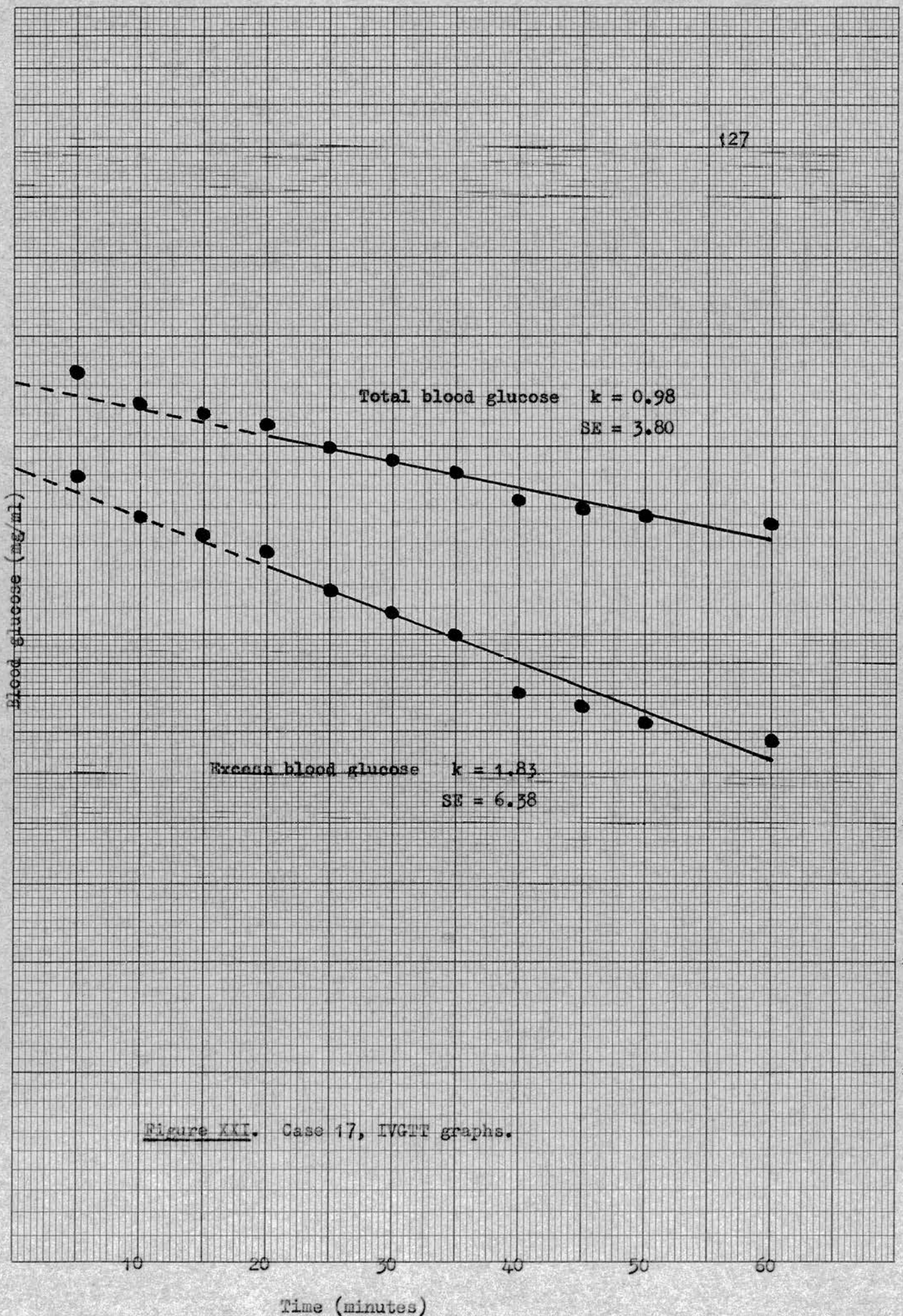

Figure XXI. Case 17, IVGTT graphs.

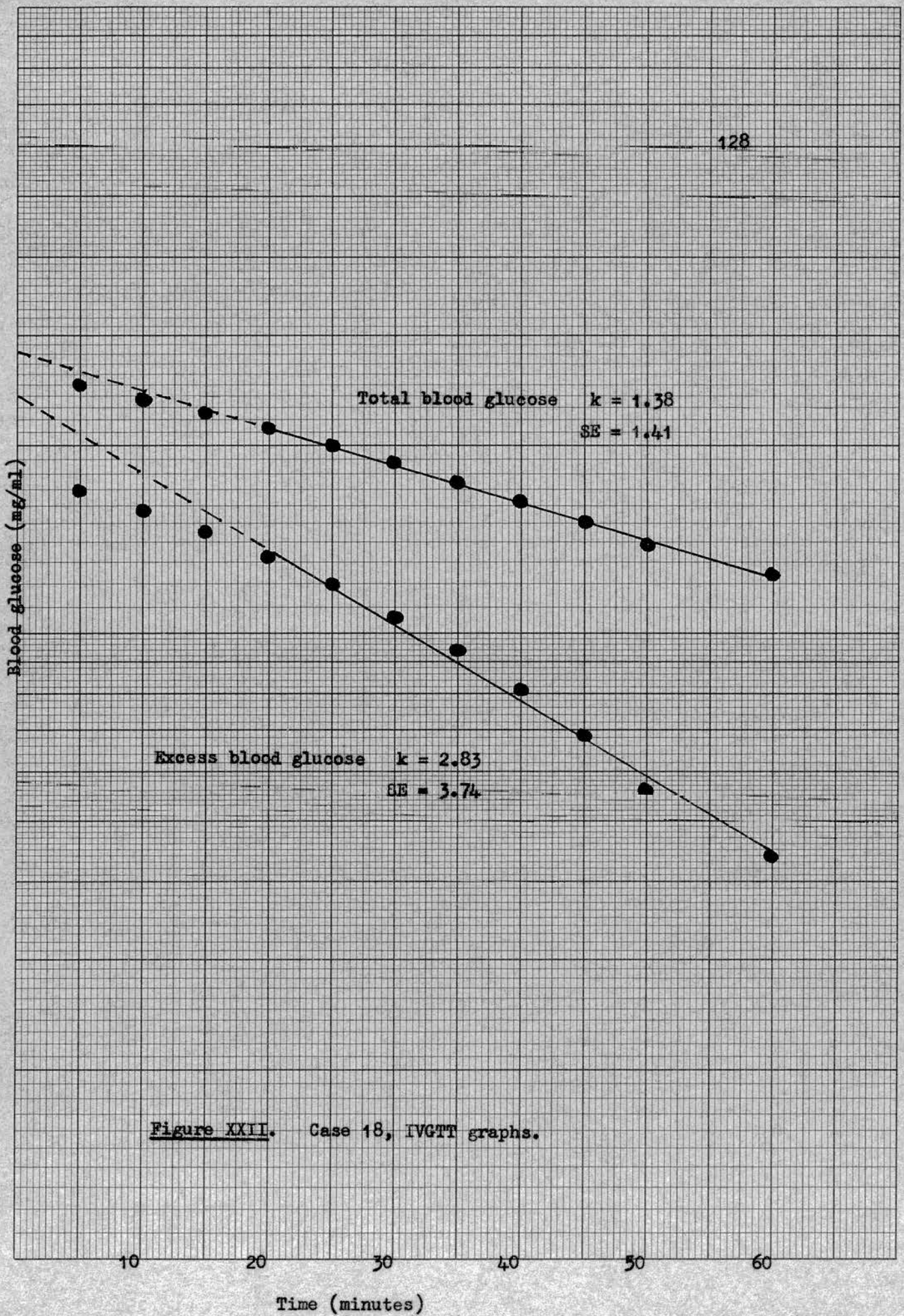

Figure XXII. Case 18, IVGTT graphs.

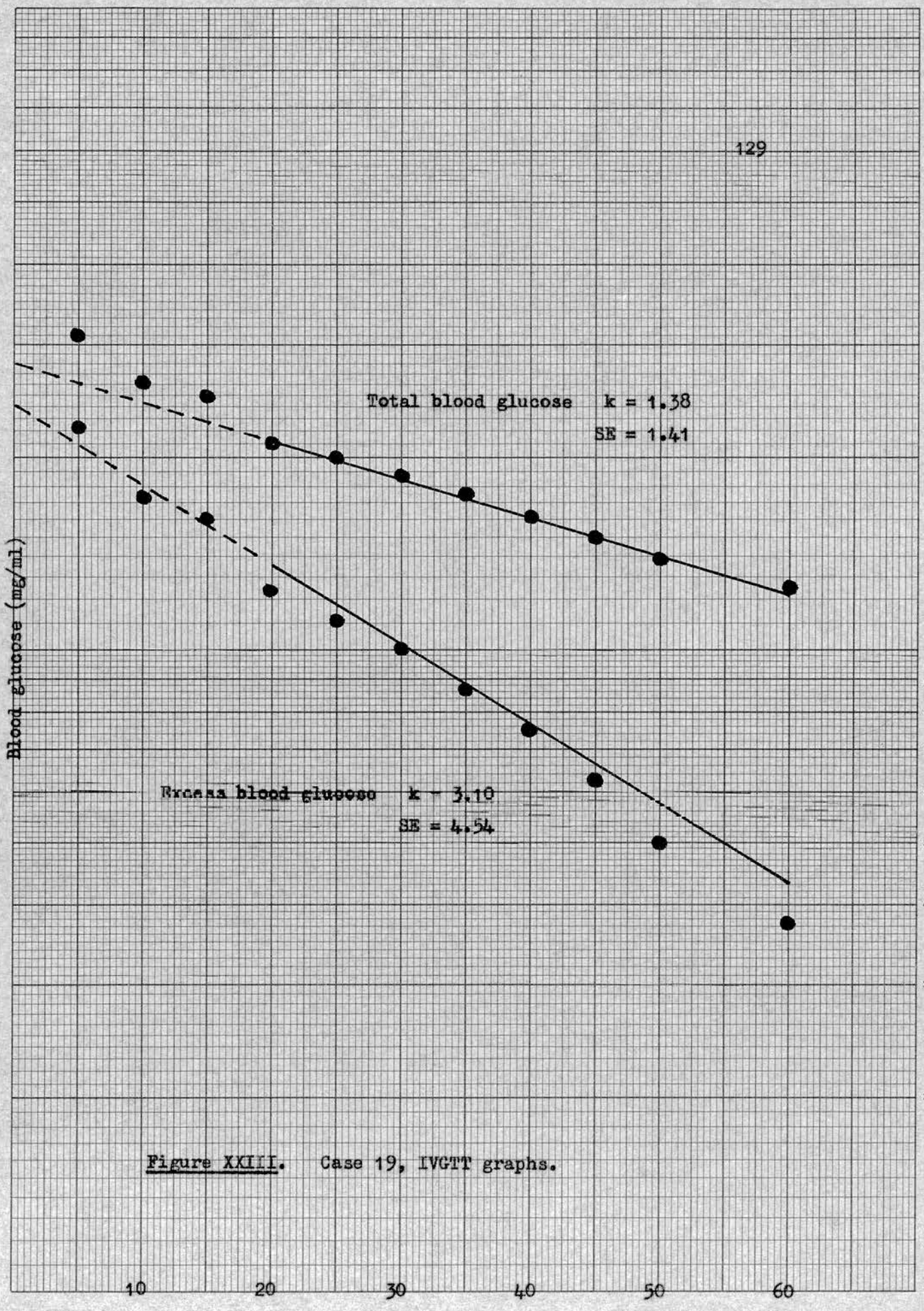

Figure XXIII. Case 19, IVGTT graphs.

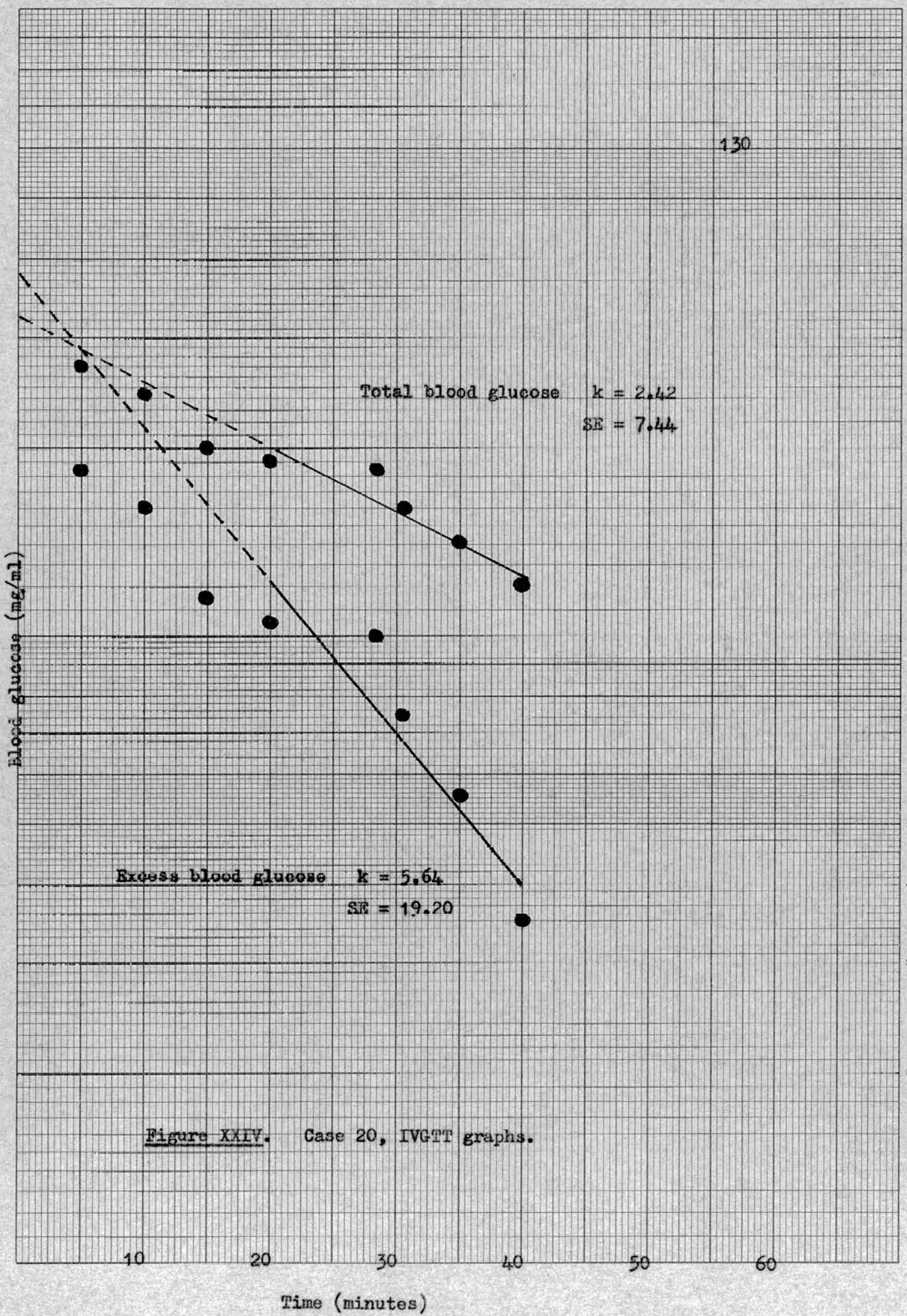

Figure XXIV. Case 20, IVGTT graphs.

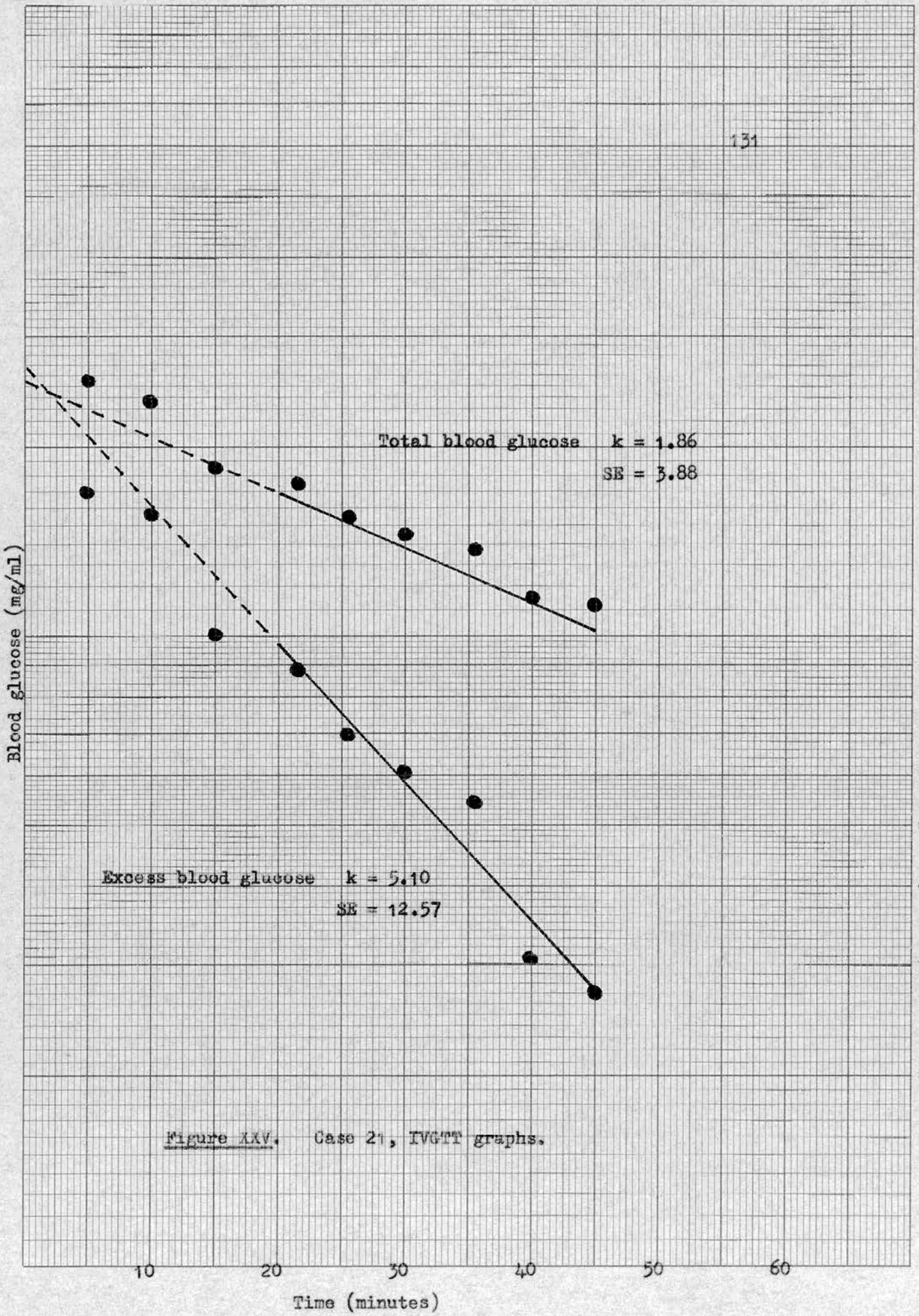

Figure XXV. Case 21, IVGTT graphs.

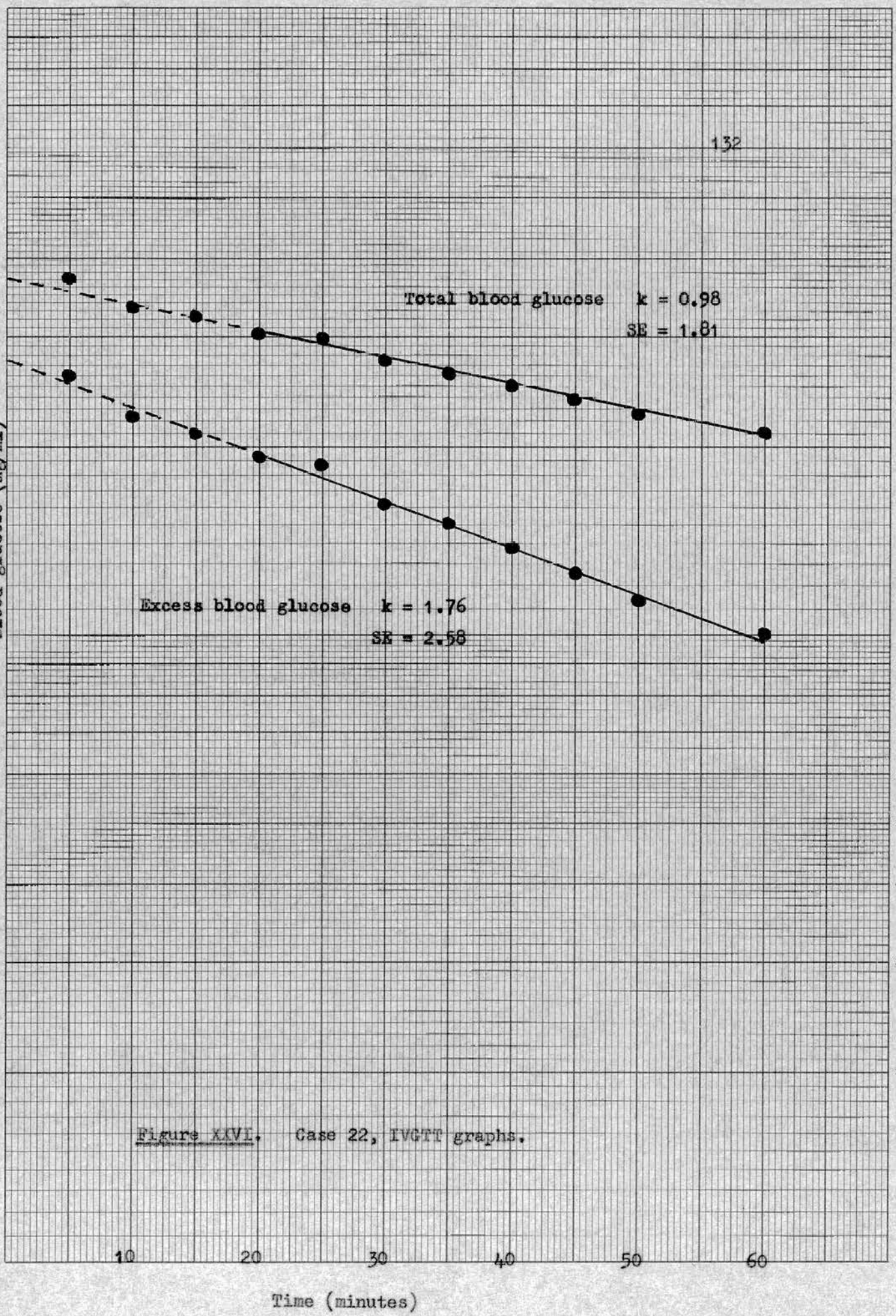

Figure XXVI. Case 22, IVGTT graphs.

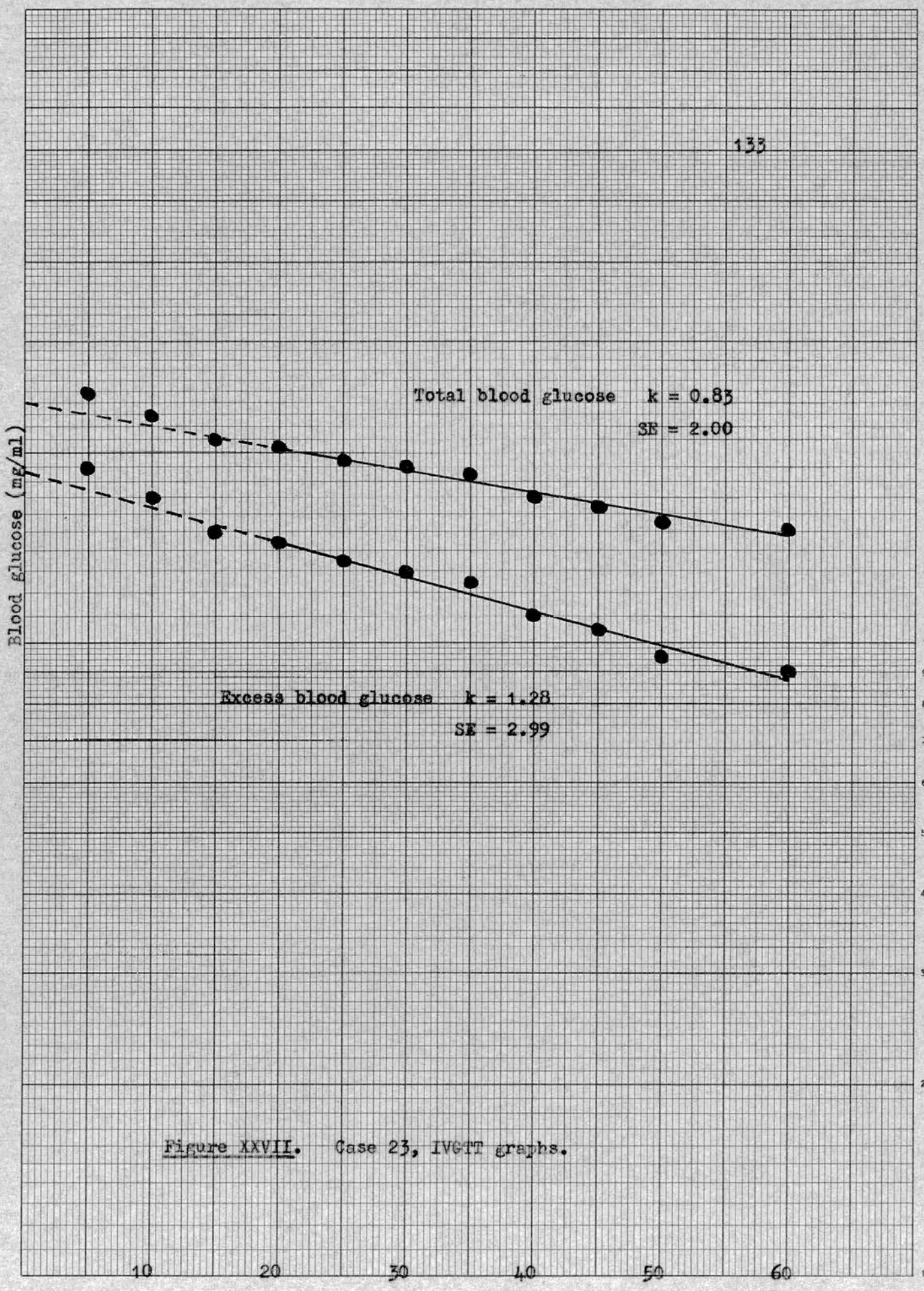

Figure XXVII. Case 23, IVGTT graphs.

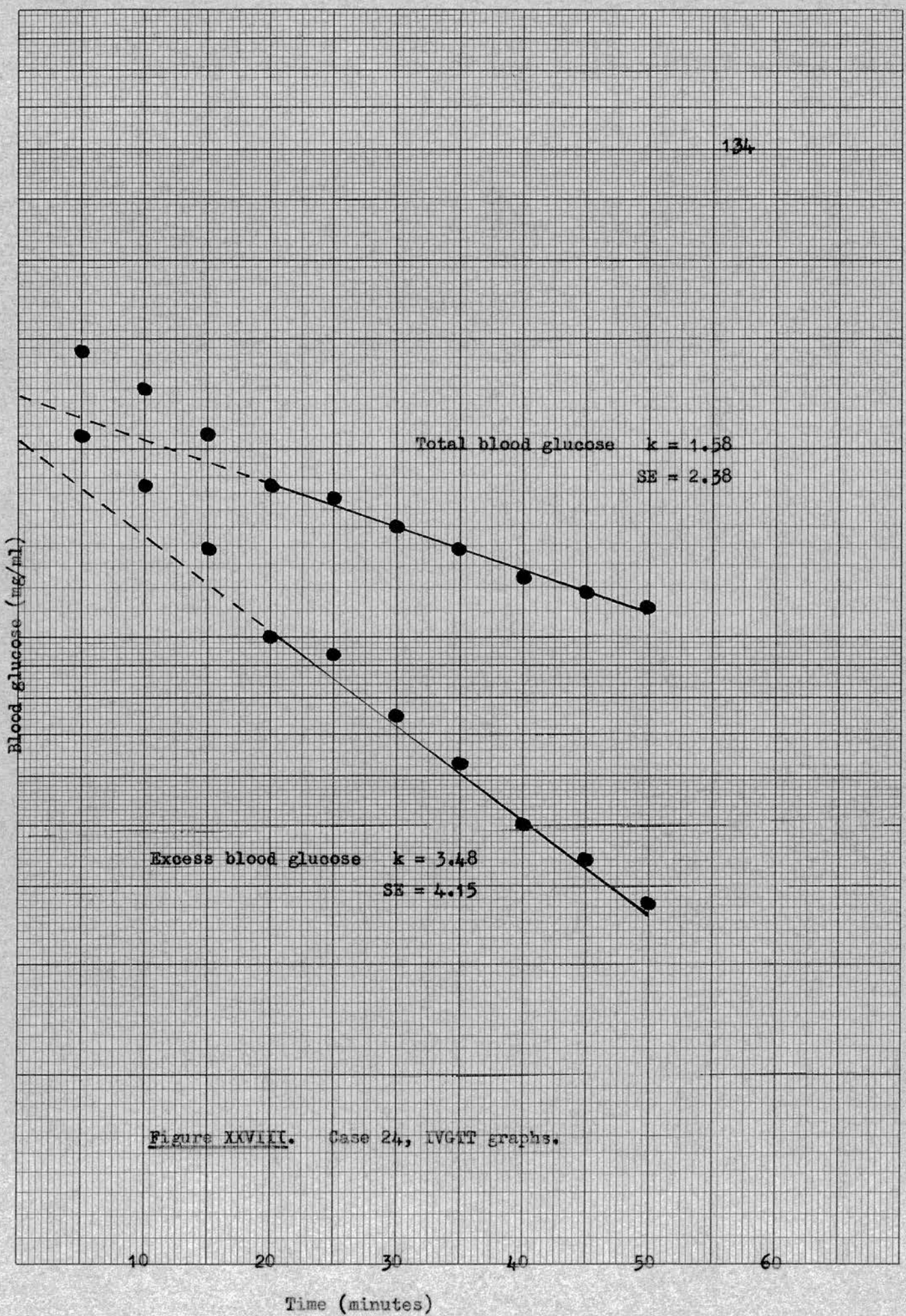

Figure XXVIII. Case 24, IVGTT graphs.

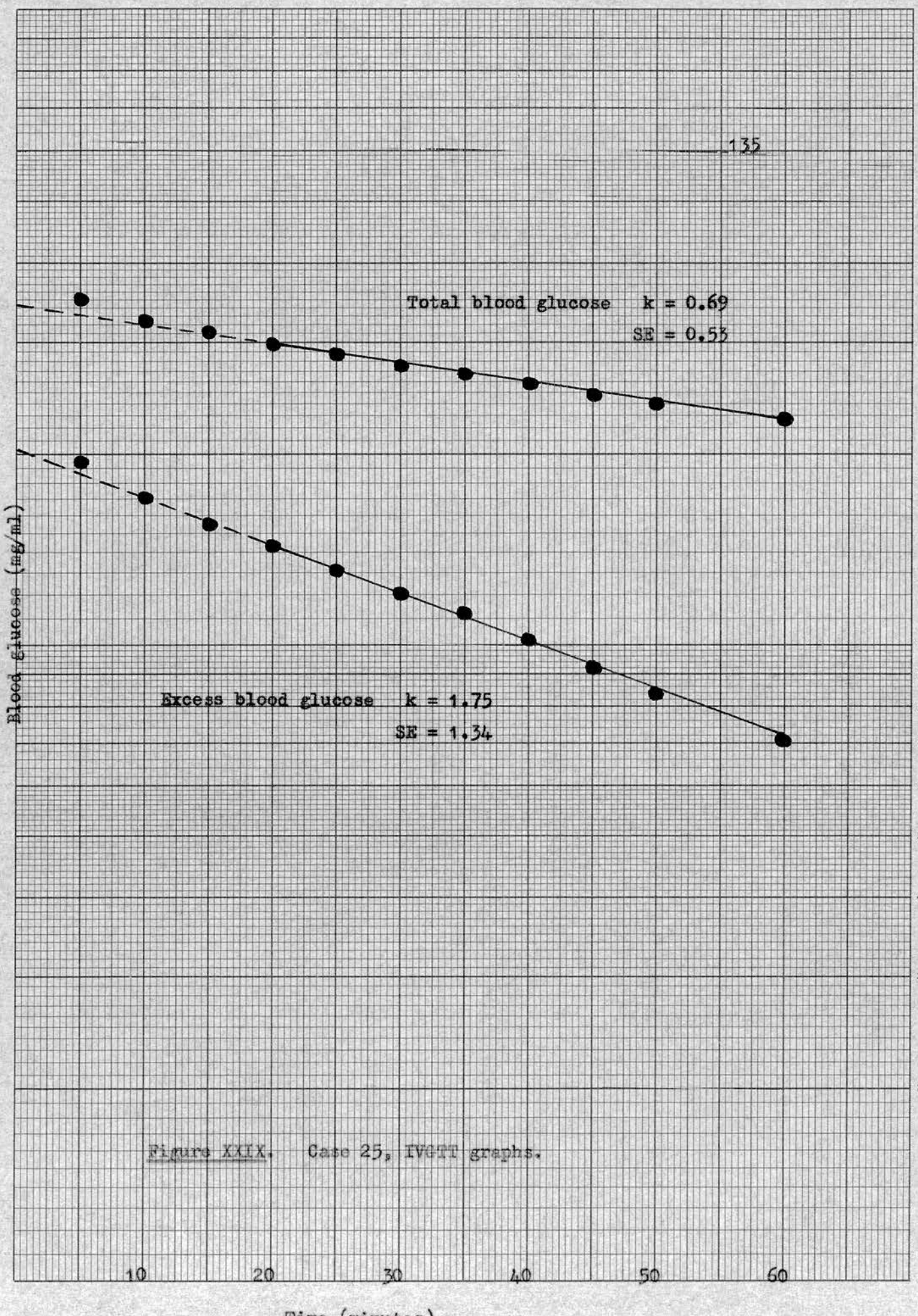

Figure XXIX. Case 25, IVGTT graphs.

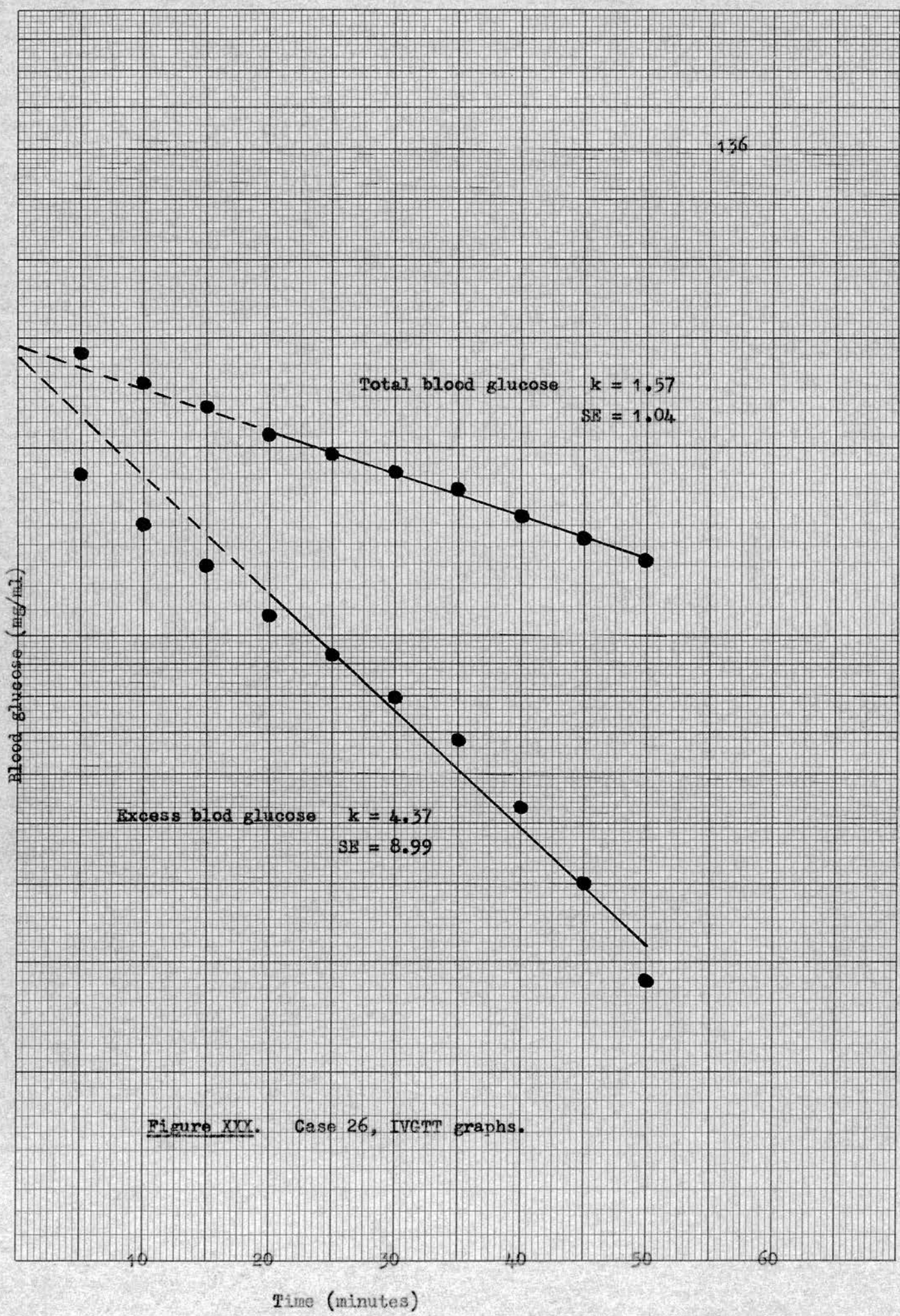

Figure XXX. Case 26, IVGTT graphs.

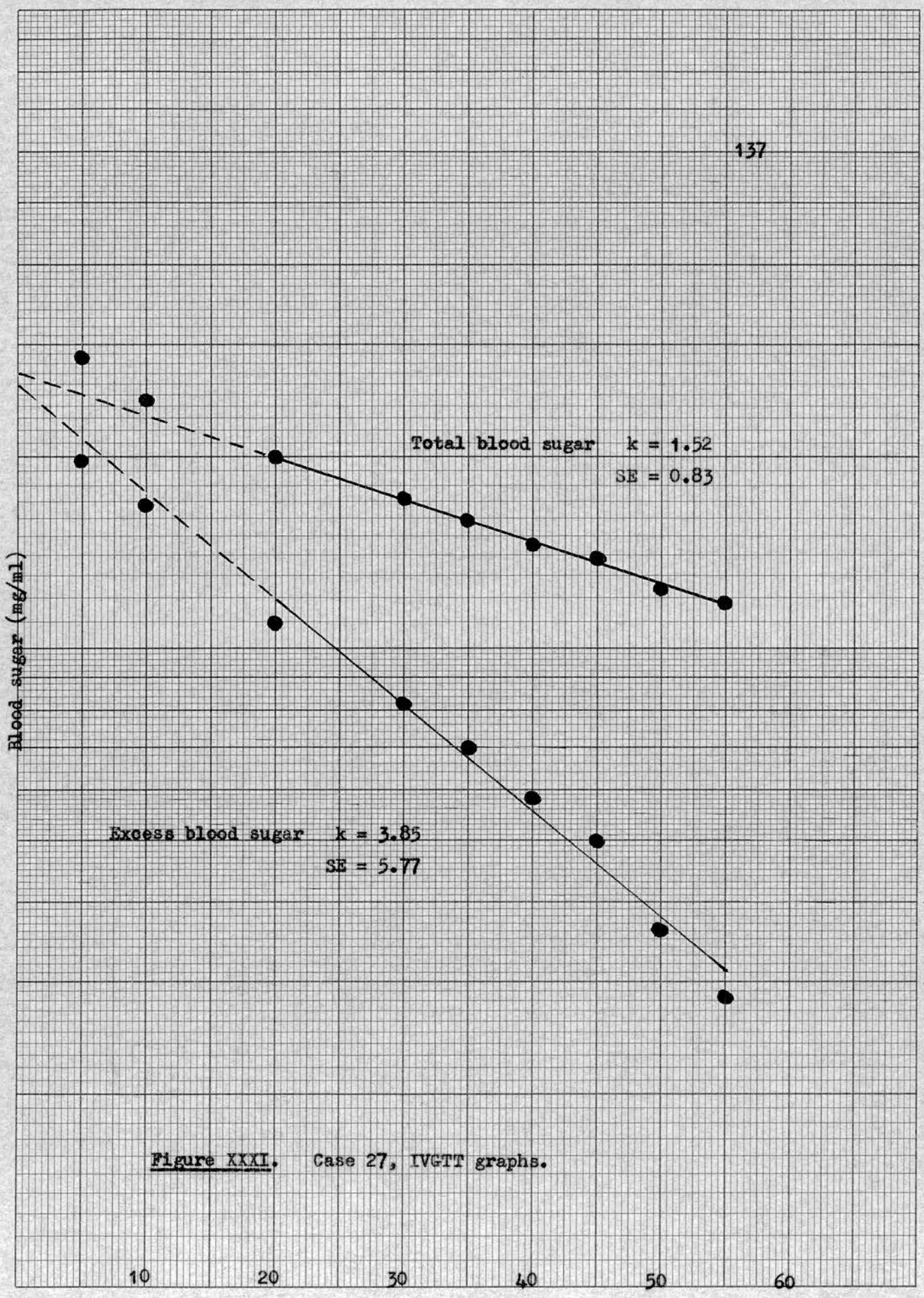

Figure XXXI. Case 27, IVGTT graphs.

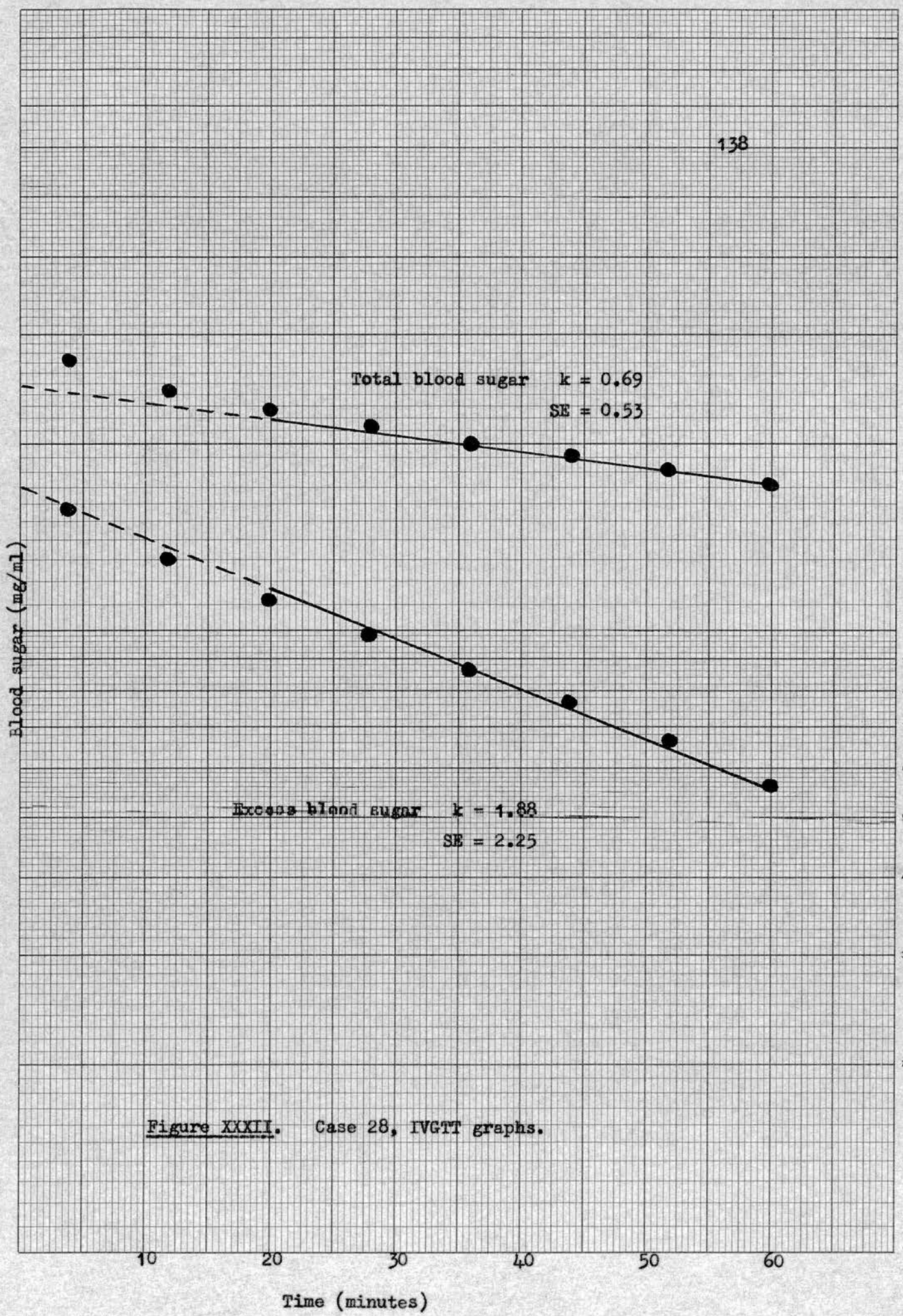

Figure XXXII. Case 28, IVGTT graphs.

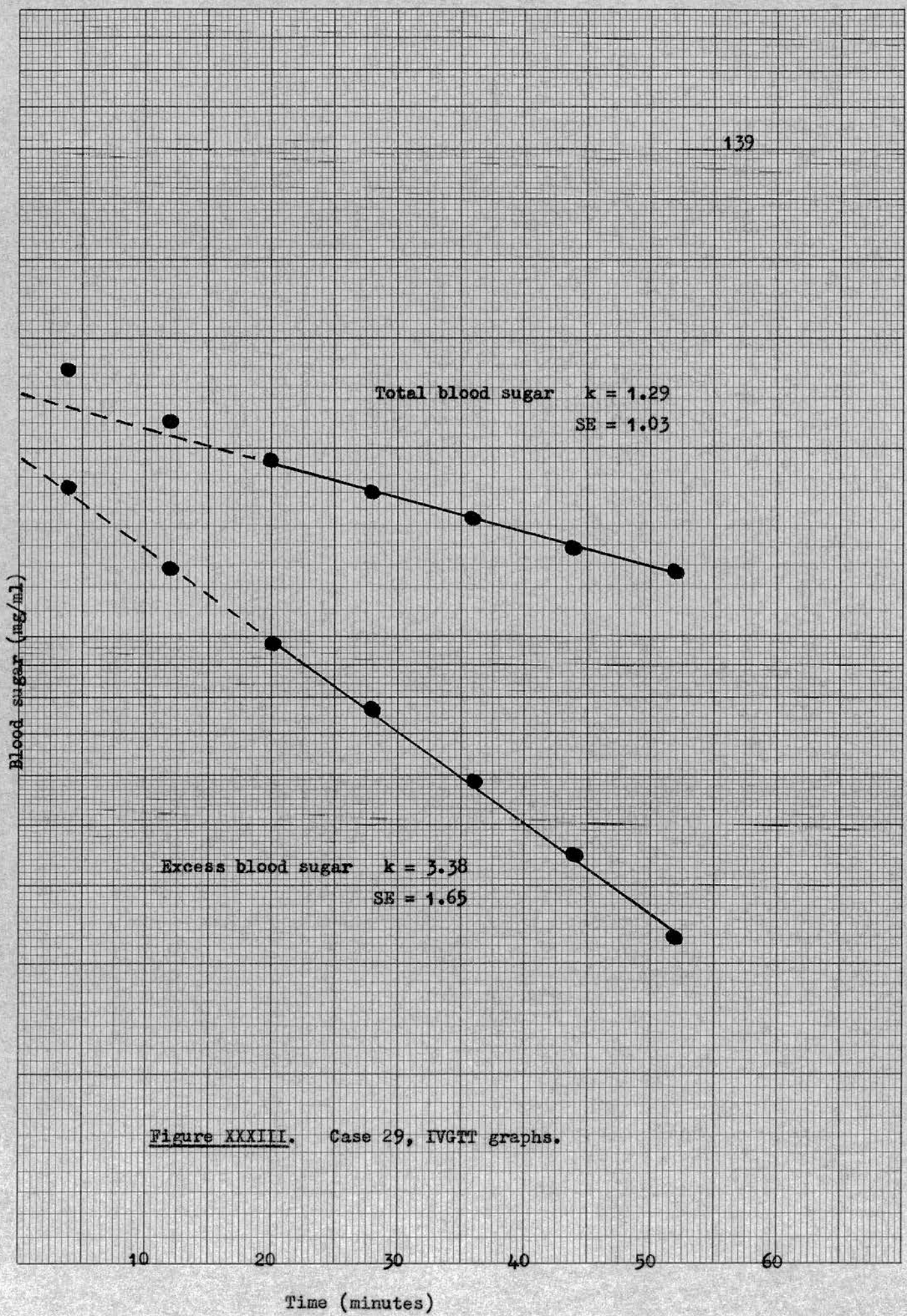

Figure XXXIII. Case 29, IVGTT graphs.

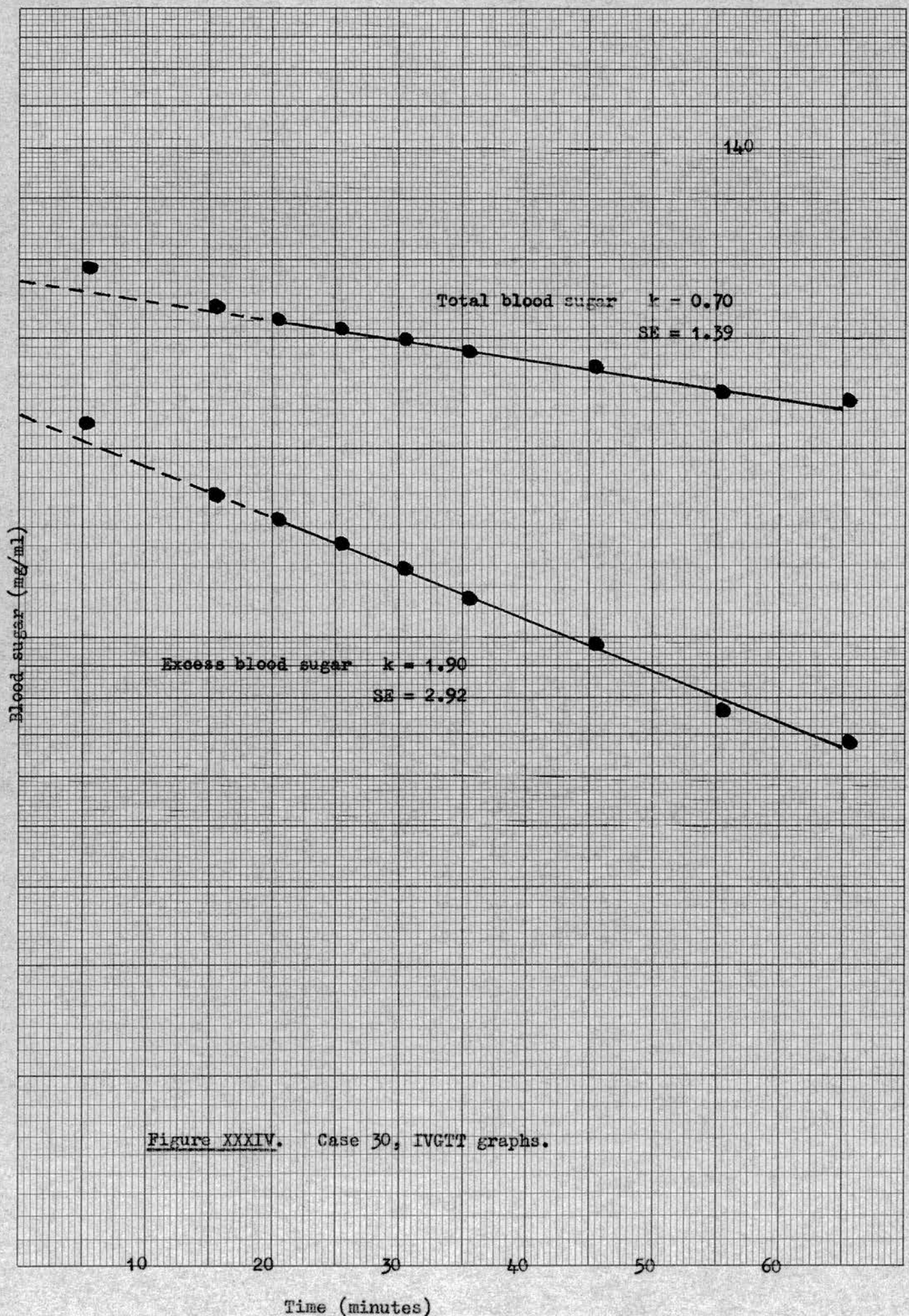

Figure XXXIV. Case 30, IVGTT graphs.

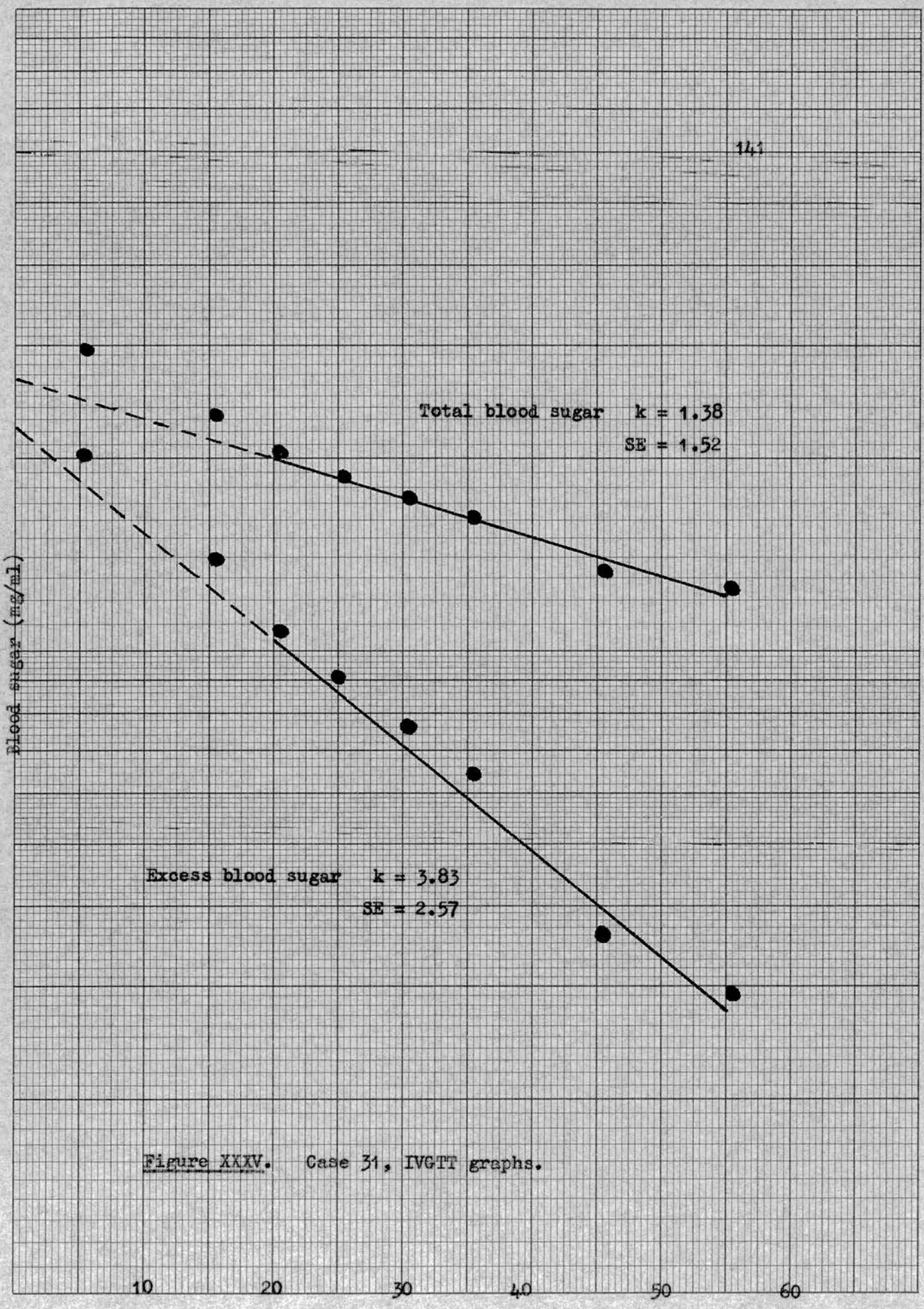

Figure XXXV. Case 31, IVGTT graphs.

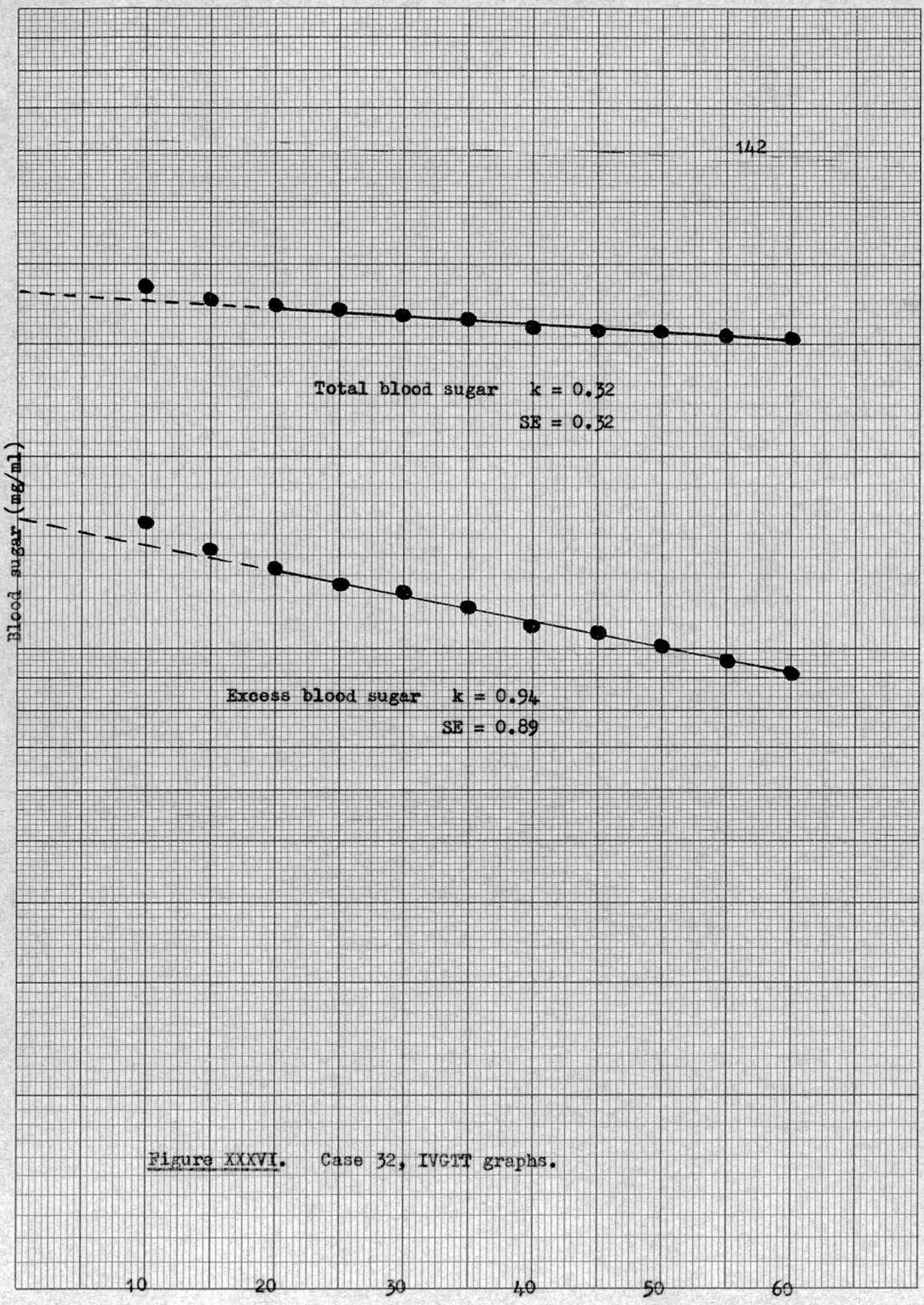

Figure XXXVI. Case 32, IVGTT graphs.

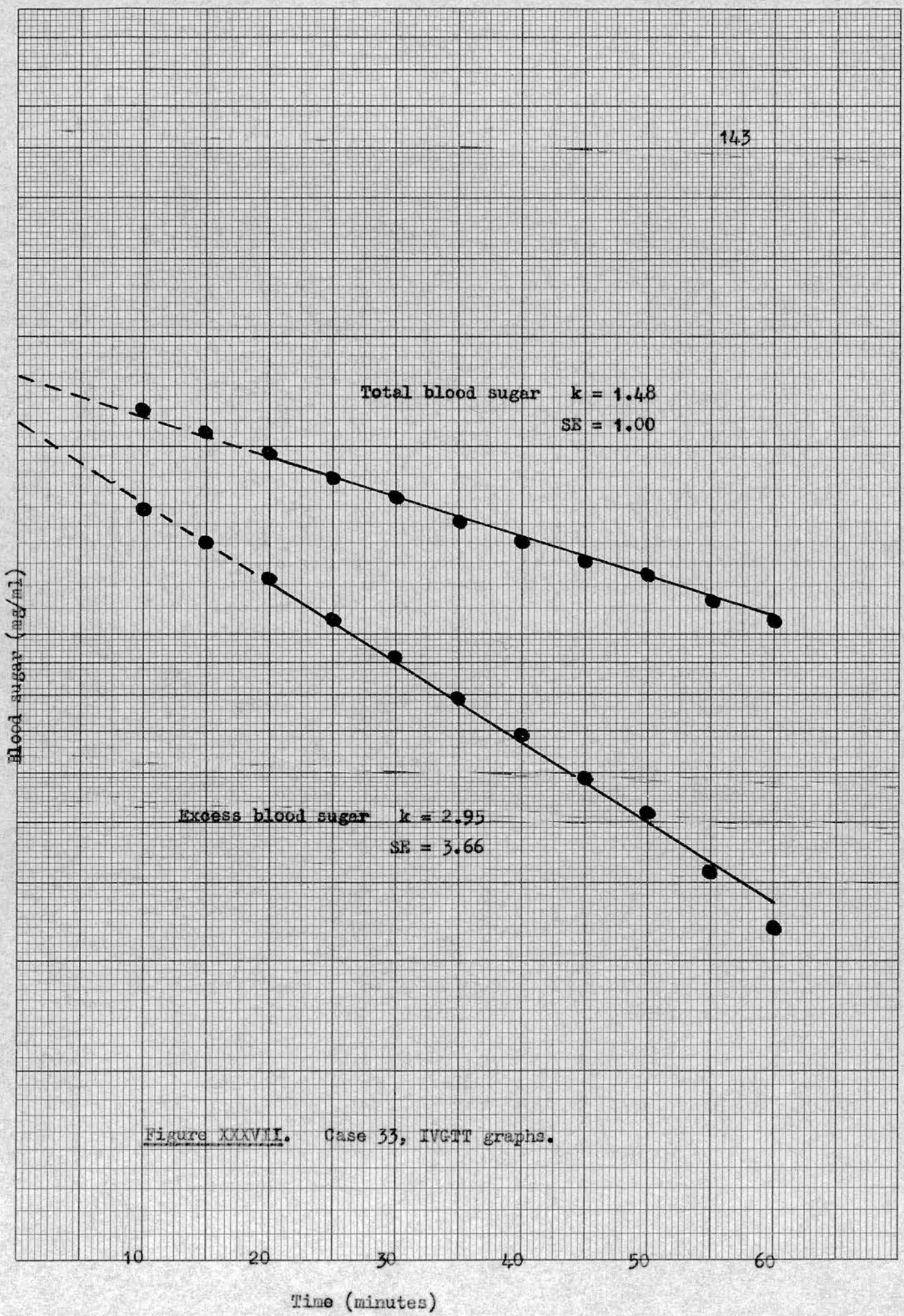

Figure XXXVII. Case 33, IVGTT graphs.

Simple Test

Table VII shows the difference between k values calculated from all valid points excluding the first three and those calculated from the 20, 40 and 60 minute points only (referred to as k'). In each case both "total" and "excess" ($S_\infty = S_f$) blood glucose values have been used. It will be seen that when "total" blood glucose is considered the percentage difference between k and k' is small in most cases, the mean difference being 5.7% (Standard Deviation $\pm$ 4.3).

If "excess" blood glucose is used the mean percentage difference between k and k' is somewhat greater (6.6%) and the variation in the degree of change from test to test is also greater (Standard Deviation $\pm$ 8.5).

Case No.	Initials	Age (yrs)	Sex	Build	Complaint	Ambulant(A) or bed(B) patient	Grade	k(T)	k'(T)	Difference (%)	k(E)	k'(E)	Difference (%)
1	M.W.*	67	M	Obese	Known diabetic	A	D1	0.62	0.62	0.0	1.25	1.25	0.0
2	E.McD.*	67	F	Obese	Known diabetic	A	D1	0.73	0.78	6.6	1.72	1.85	7.3
3	A.D.*	58	F	Obese	Known diabetic	A	D1	0.90	0.86	4.5	1.80	1.73	4.1
4	H.H.	58	F	Obese	Known diabetic	A	D2	0.77	0.74	4.0	4.47	3.47	25.2
5	M.B.	66	F	Obese	Known diabetic	A	D2	0.90	0.88	2.2	2.58	2.60	0.4
6	G.McR.	61	M	Obese	Popliteal artery embolism	B	D1	0.99	0.92	7.3	1.82	1.73	5.1
7	W.W.*	77	M	Average	Known diabetic	A	D1	0.73	0.74	1.4	1.34	1.38	2.9
8	C.F.	59	M	Average	Intermittent claudication	A	D1	0.74	0.72	2.8	1.47	1.45	1.4
9	D.McA.*	74	M	Average	Known diabetic	A	D1	0.70	0.68	2.9	1.14	1.10	3.6
10	P.B.	66	M	Average	Weight loss	B	D2	0.65	0.72	10.2	1.58	1.73	9.1
11	A.M.	51	M	Thin	Known diabetic	A	D2	0.46	0.43	6.7	1.86	1.73	7.2
12	E.B.	58	F	Thin	Polyuria and thirst	A	D2	0.55	0.56	1.8	1.90	1.91	0.5

Table VII. Brief details and k values:- Cases 1 - 12.

Notes : D1 = Mild diabetic
D2 = Moderately severe diabetic
ND = Non-diabetic
* = Recieving chlorpropamide
k(T) = k(Total)
k(E) = k(Excess)
k = k obtained from all valid points excluding the first 3
k' = k obtained from the 20, 40 and 60 minute points only.

Case No.	Initials	Age (yrs)	Sex	Build	Complaint	Ambulant(A) or bed(B) patient	Grade	k(T)	k'(T)	Difference (%)	k(E)	k'(E)	Difference (%)
13	H.D.	46	M	Obese	Panic attacks	A	ND	1.65	1.34	16.5	4.00	2.73	37.8
14	A.B.	57	M	Average	Palpitations	A	ND	1.40	1.55	10.2	3.78	3.81	0.8
15	M.B.	57	M	Average	Mesenteric artery thrombosis	A	ND	0.91	1.02	11.4	1.45	1.61	10.5
16	D.T.	23	M	Average	Healthy volunteer	A	ND	1.56	1.49	4.6	3.27	3.21	1.9
17	R.W.	77	M	Average	Glycosuria	A	ND	0.98	0.93	5.2	1.83	1.73	5.6
18	J.S.	68	M	Average	Intermittent claudication	A	ND	1.38	1.33	3.7	2.83	2.74	3.2
19	J.G.	62	M	Average	Intermittent claudication	A	ND	1.38	1.33	3.7	3.10	3.01	2.9
20	B.W.	40	F	Average	Healthy volunteer	A	ND	2.42	2.30	5.1	5.64	5.49	2.7
21	L.L.	25	F	Average	Healthy volunteer	A	ND	1.86	2.19	16.3	5.10	5.70	11.1
22	P.R.	65	M	Thin	Weight loss	A	ND	0.98	0.91	7.4	1.76	1.65	6.5
23	M.E.	59	M	Thin	Intermittent claudication	A	ND	0.83	0.78	6.2	1.28	1.19	7.3
24	B.M.	22	M	Thin	Diarrhoea	A	ND	1.58	1.68	6.1	3.48	3.47	0.3
						Mean				5.7			6.6
						Standard deviation				± 4.3			± 8.5

Table VII (continued). Brief details and k values:- Cases 13 - 24.

Notes : ND = Non-diabetic

k(T) = k(Total) k(E) = k(Excess)

k = k obtained from all valid points excluding the first 3

k' = k obtained from the 20, 40 and 60 minute points only.

Range of k values for Diabetic and Non-diabetic subjects

Tables VIII and IX record brief details respectively of diabetic and non-diabetic subjects in the larger series studied by means of the simple (3 point) test. In each case k has been calculated for both "total" and "excess" blood glucose.

Figures XXXVIII and XXXIX show graphically the ranges of k values respectively for "total" and "excess" blood glucose. In each figure diabetic and non-diabetic ranges have both been shown and k values (obtained from the same three blood glucose points - see Table VII) for Cases 1 - 24 have also been included.

In this series the main range of k values obtained from "total" blood glucose figures in diabetics is from 0.20 to 1.01 (one value lying above this range - k value 1.73) and for non-diabetics is from 0.60 to 2.74 (one value lying below this range - k value 0.44).

Using "excess" blood glucose figures the main range of k values for diabetics is from 0.40 to 2.04 (seven values lying above this, extending up to 4.08) and for non-diabetics is from 1.52 to 7.41 (three values lying below this, extending down to 0.77).

In both figures, therefore, there are a few points which lie somewhat outside the main ranges but the scatter is rather more pronounced in Figure XXXIX ("excess" blood glucose) than in Figure XXXVIII ("total" blood glucose). The overlap between diabetic and non-diabetic ranges is about the same in both Figure XXXVIII and

Figure XXXIX. Excluding those values well outside the main ranges this overlap is from 0.60 to 1.01 (39 individuals, 21 diabetics and 18 non-diabetics) in Figure XXXVIII and from 1.52 to 2.04 (35 individuals, 13 diabetics and 22 non-diabetics) in Figure XXXIX.

No.	Initials	Age (yrs)	Sex	Build	Complaint	Ambulant(A) or bed(B) patient	Grade	k (total)	k (excess)
34	M.O'C.	54	M	Obese	Cholecystectomy	A	1	0.72	1.67
35	J.D.	55			Epistaxis	A	1	0.48	1.16
36	M.W.	63			Herpes zoster	A	1	0.46	1.48
37	R.D.	68			Thirst and polyuria	A	1	0.36	1.28
38	J.W.*	49			Known diabetic	A	1	0.65	1.11
39	B.S.*	62			Known diabetic	A	1	0.33	1.04
40	B.F.*	80			Known diabetic	A	1	0.55	1.01
41	W.McD.	81			Leg oedema	B	1	0.48	1.07
42	H.W.	74			Gangrene of toe	B	1	0.38	0.63
43	A.W.	76			Herniorrhaphy	A	2	0.67	3.47
44	M.W.	59			Thirst and polyuria	A	2	0.41	1.71
45	E.J.*	84	F	Obese	Known diabetic	A	1	0.69	2.75
46	P.A.	55			Glycosuria	A	1	0.48	1.49
47	J.R.*	64			Known diabetic	A	1	0.31	0.70
48	J.C.	52			Ischaemic toe	A	1	0.32	0.42
49	J.O'T.	60			Glycosuria	A	1	0.99	1.38
50	S.C.	71			Cerebral thrombosis	A	1	1.01	2.50
51	M.Q.*	49			Known diabetic	A	1	0.59	1.50
52	M.L.	76			Glycosuria	A	1	0.23	0.56
53	M.D.	69			Depression	A	1	0.28	0.91
54	M.G.	64			Abdominal pain	B	1	1.73	3.47
55	A.L.	75			Epithelioma of leg	B	1	0.41	0.89
56	M.S.*	72			Ischaemia of foot	B	1	0.28	0.56
57	M.R.	71			Known diabetic	A	2	0.50	0.71
58	F.M.	75			Cerebral ischaemia	A	2	0.43	1.11
59	S.G.	65			Known diabetic	A	2	0.24	0.40
60	H.H.	58			Known diabetic	A	2	0.47	1.73

Table VIII. Brief details and k values for diabetic subjects, using the simple test. Cases 34 - 60.

(Patients marked * were recieving chlorpropamide.)

(Diabetic grades : 1 = Mild,
2 = Moderately severe.)

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No.	Initials	Age (yrs)	Sex	Build	Complaint	Ambulant(A) or bed(B) patient	Grade	k (total)	k (excess)
61	W.G.*	63	M	Average	Known diabetic	A	1	0.29	0.50
62	M.W.	39			Thirst and polyuria	A	1	0.26	0.77
63	S.S.	57			Glycosuria	A	1	0.72	1.52
64	P.M.	79			Popliteal aneurism	B	1	0.46	1.24
65	J.B.	61			Hemiplegia	B	1	0.56	1.16
66	T.O'C.	67			Intermittent claudication	B	1	0.86	1.36
67	P.McC.	62			Known diabetic	A	2	0.34	0.97
68	S.W.	32			Known diabetic	A	3	0.29	0.99
69	M.H.	59	F	Average	Glycosuria	A	1	0.72	1.37
70	S.R.	45			Known diabetic	A	2	0.51	1.49
71	G.W.	65	M	Thin	Intermittent claudication	A	1	0.41	0.66
72	J.S.	46			Thirst and polyuria	A	1	0.58	1.71
73	H.W.*	78			Known diabetic	A	1	0.91	4.08
74	W.H.	61			Myocardial infarction	B	1	0.20	0.55
75	J.J.	65			Chronic nephritis	B	1	0.75	1.24
76	J.N.	65			Intermittent claudication	B	1	0.22	0.54
77	F.T.	70			Weakness of legs	A	2	0.33	1.15
78	R.M.	79			Known diabetic	A	3	0.40	1.59
79	J.L.	72			Cerebral ischaemia	A	3	0.36	1.03
80	F.H.	81	F	Thin	Ischaemic foot	B	1	0.39	0.74
81	R.B.	26			Known diabetic	A	3	0.36	1.12
82	M.S.	70			Thirst and polyuria	A	3	0.35	1.29
83	C.W.	66			Known diabetic	A	3	0.42	2.04

Table VIII (continued). Brief details and k values for diabetic subjects, using the simple test. Cases 61 - 83.
(Patients marked * were recieving chlorpropamide.)
(Diabetic grades : 1 = Mild,
2 = Moderately severe,
3 = Severe.)

No.	Initials	Age (yrs)	Sex	Build	Complaint	Ambulant(A) or bed(B) patient	Grade	k (total)	k (excess)
84	J.W.	63	M	Obese	Peripheral neuritis	A	ND	0.87	2.20
85	A.S.	30			Obesity	A	ND	0.69	2.12
86	T.D.	65			Ischaemia of foot	B	ND	2.65	3.89
87	J.C.	83			Ischaemic leg ulcer	B	ND	0.70	1.87
88	E.W.	57	F	Obese	Psoriasis	A	ND	1.06	1.82
89	M.K.	38			Varicose leg ulcers	A	ND	1.23	2.85
90	A.H.	50			Intermittent claudication	A	ND	1.36	2.70
91	D.L.	38			Fainting attacks	A	ND	1.66	3.46
92	E.C.	53			Ischaemic leg ulcers	B	ND	1.52	3.13
93	E.B.	72			Ischaemic foot ulcers	B	ND	0.78	1.54
94	A.O'G.	75			Ischaemia of foot	B	ND	0.74	1.58
95	M.D.	62			Intermittent claudication	B	ND	0.72	1.72
96	P.G.	55	M	Average	Glycosuria	A	ND	2.03	3.87
97	J.W.	44			Angioneurotic oedema	A	ND	1.08	3.01
98	J.G.	61			Intermittent claudication	A	ND	1.28	2.73
99	H.N.	16			Kleine-Levin syndrome	A	ND	0.71	1.61
100	J.K.	61			Intermittent claudication	A	ND	0.44	0.77
101	F.M.	21			Healthy student	A	ND	1.28	2.74
102	C.D.	21			Healthy student	A	ND	2.13	6.01
103	W.A.	21			Healthy student	A	ND	1.40	3.00
104	J.McD.	24			Hypertension	A	ND	0.89	1.58
105	H.J.	52			Cerebral thrombosis	A	ND	1.28	3.25
106	R.R.	46			Syncope	A	ND	1.55	3.47
107	J.L.	48			Duodenal ulcer	A	ND	1.27	2.93
108	J.C.	54			Carotid stenosis	A	ND	0.94	2.45

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Table IX. Brief details and k values for non-diabetic subjects, using the simple test. Cases 84 - 108.

(ND = Non-diabetic)

No.	Initials	Age (yrs)	Sex	Build	Complaint	Ambulant(A) or bed(B) patient	Grade	k (total)	k (excess)
109	W.H.	64	M	Average	Femoral artery aneurism	B	ND	1.20	1.94
110	T.M.	61			Ischaemia of foot	B	ND	1.02	1.79
111	M.O'R.	65			Aneurism of aorta	B	ND	0.80	1.55
112	D.S.	46			Chronic bronchitis	B	ND	1.02	1.65
113	W.B.	62			Intermittent claudication	B	ND	0.85	2.23
114	A.C.	73			Ischaemia of feet	B	ND	0.80	1.73
115	G.G.	34	F	Average	Low back pain	A	ND	1.39	3.01
116	E.B.	37			Disc sciatica	A	ND	1.09	2.09
117	E.D.	55			Leg cramps	A	ND	2.35	4.90
118	M.C.	52			Pruritus vulvae	A	ND	1.41	2.95
119	M.G.	56			Abdominal pain	A	ND	1.87	4.82
120	J.F.	16			Abdominal pain	A	ND	1.08	1.98
121	J.M.	21			Healthy student	A	ND	2.64	5.00
122	M.T.	56			Paraesthesiae of feet	A	ND	0.83	1.52
123	A.W.	49			Thirst and polyuria	A	ND	1.11	1.53
124	F.C.	45	M	Thin	Blackouts	A	ND	1.40	2.29
125	P.C.	69			Ischaemia of leg	A	ND	1.19	1.89
126	J.M.	64			Ischaemic leg ulcer	A	ND	0.88	1.78
127	C.D.	54			Carotid stenosis	A	ND	1.44	2.93
128	R.S.	44			Pruritus ani	A	ND	2.74	7.41
129	P.R.	64			Disc sciatica	A	ND	1.27	2.34
130	G.W.	73			Intermittent claudication	A	ND	1.22	1.80
131	R.M.	45			Functional diarrhoea	A	ND	1.44	3.47
132	J.D.	73			Ischaemia of legs	B	ND	1.03	1.90
133	W.T.	67			Ischaemia of foot	B	ND	0.60	1.02

Table IX (continued). Brief details and k values for non-diabetic subjects, using the simple test. Cases 109 - 133.
(ND = Non-diabetic)

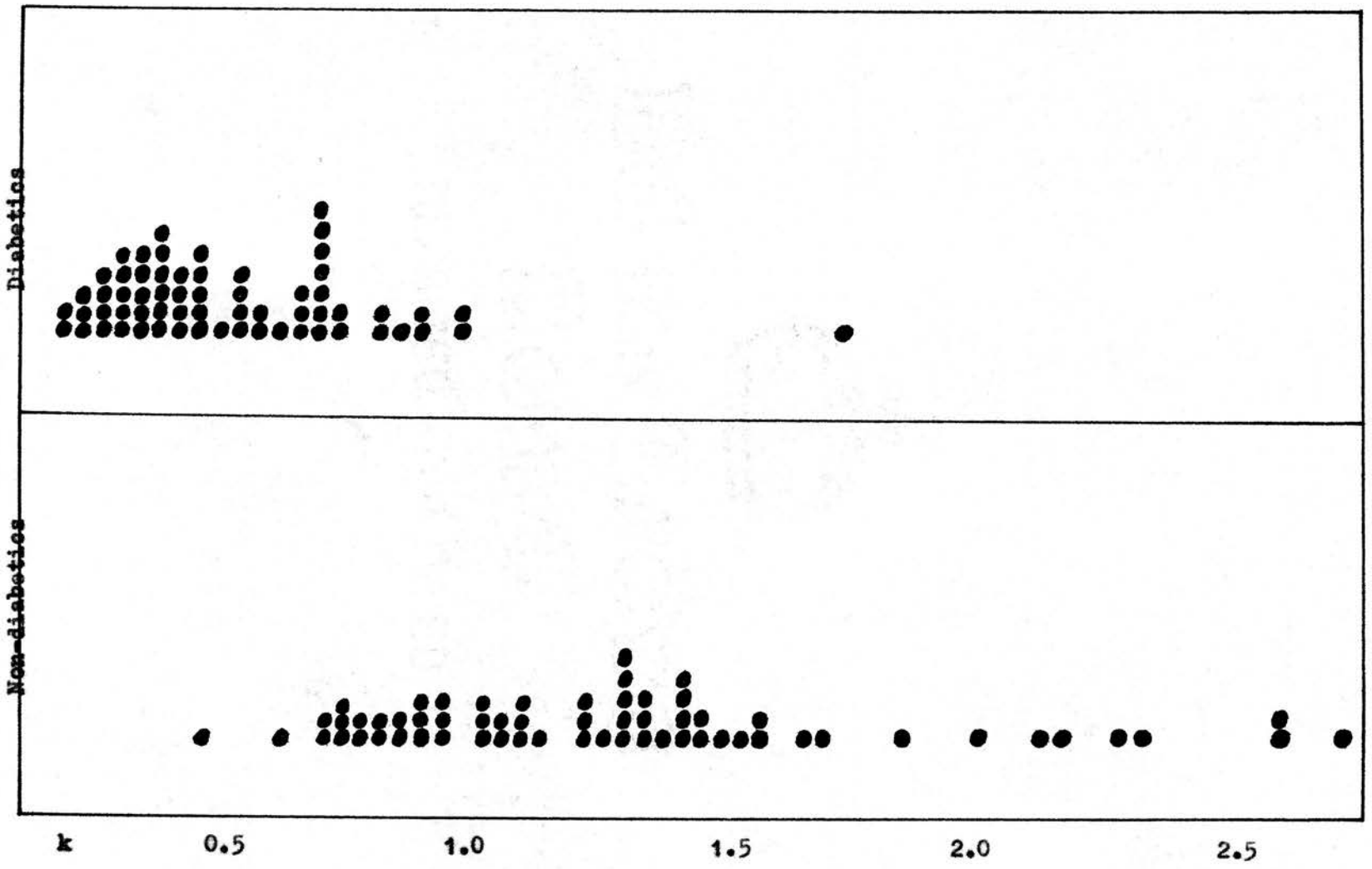


Figure XXXVIII. Range of k(total) values for diabetic and non-diabetic subjects, using the simple test.

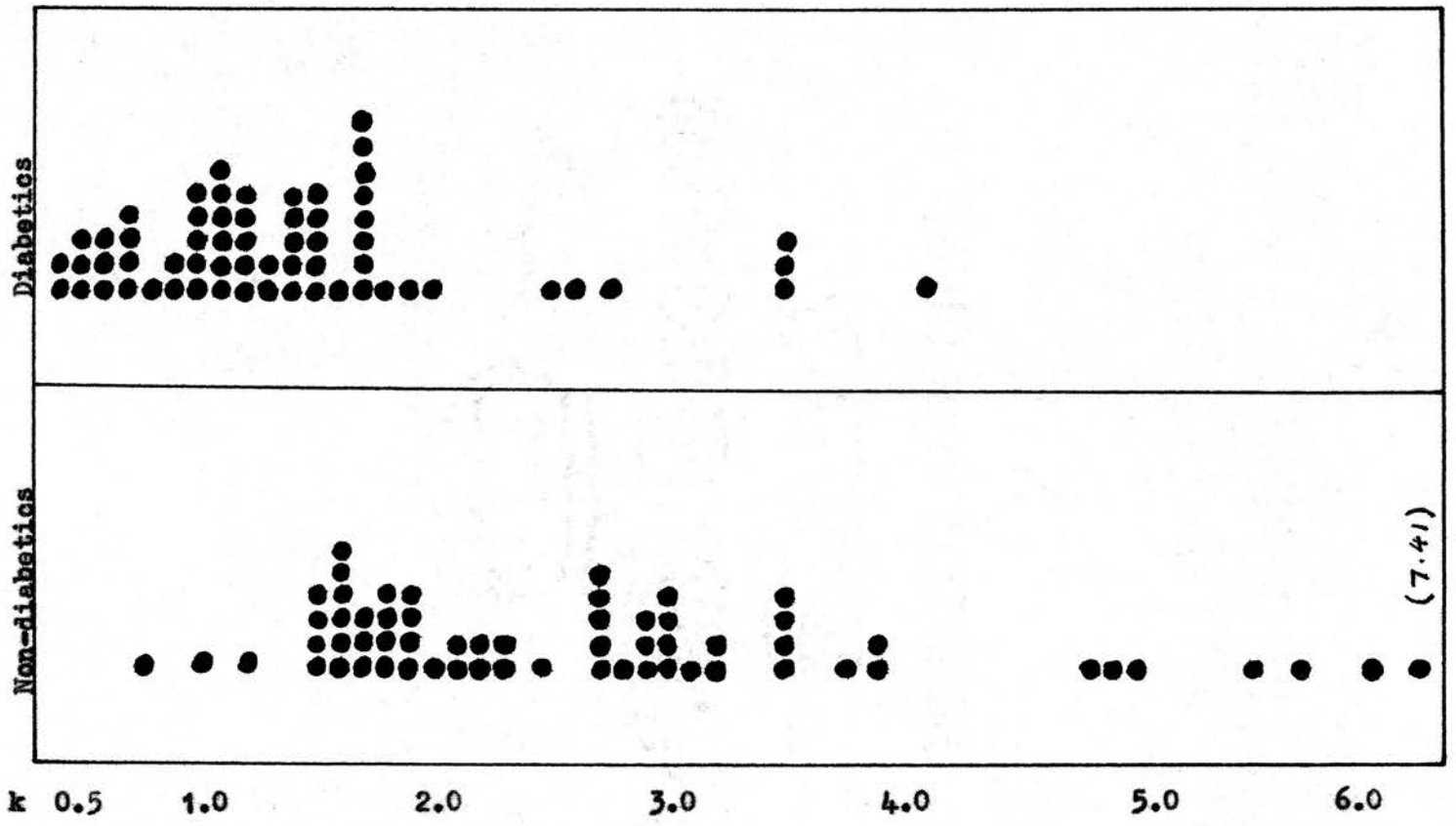


Figure XXXIX. Range of k(excess) values for diabetic and non-diabetic subjects, using the simple test.

DISCUSSION

Theoretical considerations

Duncan (1956a) and Baird and Duncan (1957, 1959) showed that if k was related to "total" blood sugar it should not alter for different glucose loads in an IVGTT nor for different fasting blood sugar levels. They claimed, however, that it did so alter, whereas if "excess" blood sugar figures were used k remained constant within at least a twofold variation of glucose dose.

They further showed that following treatment with carbutamide k obtained from "total" blood sugar figures - k ("total") - was improved, whereas k obtained from "excess" blood sugar figures - k ("excess") - remained the same as before treatment. OGTT blood sugar curves had the same configuration both before and after treatment although the curve after treatment was lower. The similarity of OGTT curves suggested to these workers that no improvement of glucose tolerance had occurred after treatment and therefore the unchanged k ("excess") was to be preferred to the improved k ("total"). Excess blood sugar was also used in this way by Jokipi and Turpeinen (1954), Mackler et al. (1952) and Scow and Cornfield (1954). Bastenie et al. (1957) found no alteration in k ("total") following carbutamide but other workers have confirmed Baird and Duncan's (1957) findings (Jensen et al. 1958, Fajans and Conn 1960, Lundbaek 1962).

There seems no reason, however, why this should not represent a real improvement in glucose metabolism (Bastenie et al. 1957,

Jensen et al. 1958, Fajans and Conn 1960, Phear 1962). Admittedly the single OGTT curve illustrated in Baird and Duncan's (1957) paper shows an identical rate of fall of blood sugar both before and after treatment, but in view of the many physiological variables capable of influencing the OGTT blood sugar curve it seems unwise to place too much reliance on this one finding.

Amatuzio et al. (1953) used "excess" blood sugar in order to eliminate any possible errors due to non-glucose reducing substances. If true glucose is measured, however, there is no need for this precaution. In any case it assumes that the quantity of non-glucose reducing substances remains constant during the whole test and this is probably not so (Mosenthal and Barry 1946).

Another approach was that of Wyngaarden et al. (1957) who related the disappearance rate from the blood stream of certain sugars to their chemical structure. The structure of glucose was said to agree well with its disappearance rate if k ("excess") was used but not if k ("total") was used.

Both Greville (1943) and Hlad et al. (1956, 1959) also used "excess" blood sugar but in their case the "excess" referred to was the difference between the observed blood sugar and a mathematical equilibrium point. This varied from 10 to 70 mg per 100 ml in different tests - even in the same individual - and was always less than the initial fasting blood sugar (S_f) in non-diabetics although usually above it in diabetics. This point was called S_∞ .

These workers claimed that their theories could be justified graphically by actually measuring the slope of an IVGTT blood sugar curve drawn on linear graph paper. Using this method, determination of the blood sugar disappearance rate was said to be independent of any mathematical or theoretical presuppositions. (On the other hand, although Hlad and Elrick (1959) used a mechanical slope-reader to obtain accurate figures from their curves, the curves themselves had to be drawn by eye and were thus liable to error. This criticism also applies to Greville (1943).) Using this technique these workers calculated k in any given IVGTT using all the points between about 5 and 90 minutes. In practice, however, one or two of the early blood sugar readings were sometimes ignored because of "systematic departures" (Greville 1943) from a straight line graph. Moreover, in nearly all cases the blood sugar had fallen to S_f or below by the end of the test.

But it has already been shown (p. 58) that the shape of the blood sugar (or blood glucose) curve following an intravenous glucose load is the result of at least four factors - dispersal and equilibration of the injected glucose, urinary loss of glucose, cell metabolism and final adjustment by normal homeostatic mechanisms. In some cases a reasonably good straight line semilogarithmic graph between blood sugar (or blood glucose) and time can be obtained as early as two minutes after glucose injection (for example, cases 1, 2, 6, 8, 10, 11, 14 of Hamilton and Stein 1942, see also cases 3, 9, 11, 14 and 18 of the present series) and glucose disappearance may in such cases

be regarded as exponential even at the beginning of the test. This relationship must, however, be broken as soon as glucose appearance (for example, from glycogenolysis) recommences. Thus Greville (1943) and Hlad et al. (1956) obtain values of k based on a composite graph of all three phases and these values will not necessarily correspond with the actual rate of cell metabolism.

Section of IVGTT slope used

It is clear that preference for "total" or "excess" blood sugar will depend largely on the time during which IVGTT blood sugar readings are considered valid for the calculation of k. It seems reasonable to ignore the later part of the slope when the "total" blood sugar has fallen to within 25 or 30 mg per 100 ml of S_f. As to the earlier part of the test Greville (1943) claimed (in spite of an occasionaly poorly-fitting early point) that the whole slope from as early as five minutes after glucose injection could be used, provided that the appropriate value of S_∞ was incorporated into the calculation. Analysis of the mean figures of Greville's own results (case 27, Table VI) shows, however, that the SE is considerably smaller (that is, there is a better straight line fit) when the first one or two points are omitted than when all valid points are used. Table VI refers, of course, to the special case when $S_\infty = 0$ but Table V shows that the SE is greater if alternative values for S_∞ are used.

Ikkos and Luft (1957) analysed their own and Amatuzio et al.'s (1953) results and came to the conclusion that the early part of an IVGTT blood sugar slope had the features of a double exponential function, one being concerned with glucose equilibration and the other with true metabolism. Provided only that part of the slope after about the 25th minute was considered, there was a good linear relationship between log "total" blood sugar and time but not between log "excess" blood sugar and time. They made the point that use of "excess" blood sugar implied that the body could distinguish between endogenous and exogenous glucose, whereas Mackler et al. (1952) had previously shown that it could not. Furthermore, it implied that the fasting blood sugar can be regarded as a constant base-line throughout the test which is probably not so (Soskin et al. 1934, Searle and Chaikoff 1952, Reichard et al. 1958).

Pryce (1958) suggested that one reason why k values altered with different doses of injected glucose might be because larger glucose loads needed longer to diffuse through the body fluids. Such differences of k as had been found could perhaps be eliminated if blood sugar measurements were only made after the 30th minute following glucose injection. West and Wood (1959) took up this idea and analysed Duncan's (1956a) figures. They demonstrated that if only the latter parts of the IVGTT graphs were considered, (that is, between about 25 and 60 minutes after glucose injection), k ("total") varied less than k ("excess") even for a twofold increase in glucose dose. In other words, k ("total") remained fairly constant within this range provided that comparison was made only

between those parts of the graphs at comparable blood sugar levels.

Nilsson (1962) in a comparative series also found that k ("total") was more reliable than k ("excess") if the latter part of the blood sugar graph was considered. Lundbaek (1962), who also preferred k ("total"), reverted to the use of all available blood sugar readings from 10 minutes onwards after glucose injection. In his case, however, a straight line was fitted to the points by eye and this is inevitably less accurate than mathematical methods.

(It should perhaps be pointed out here that while a number of variants on the simple exponential equation may be clinically useful and even highly reproducible, this does not necessarily mean that they are a true representation of the disappearance of glucose from the blood (Hlad and Elrick 1959).)

It has been suggested that different formulae should be used for diabetic and non-diabetic subjects (Baird and Duncan 1959). Certainly, hepatic glycogenolysis is excessive in the diabetic (Bastenie et al. 1957) in whom, in addition, urinary glucose loss during an IVGTT will usually be greater than in the non-diabetic. The observations of Ikkos and Luft (1957) also suggest that there is some essential difference in the nature of glucose removal from the blood in a severe diabetic from that in a non-diabetic. These workers found that in non-diabetics there was a good straight line fit of points after the 25th minute on an IVGTT semilogarithmic graph if "total" blood sugar was used but not if "excess" blood sugar was used. In

severe diabetics, however, a reasonably good straight line fit could be obtained for both "total" or "excess" blood sugar figures. Nevertheless, while differences in glucose disposal undoubtedly exist, any attempt to provide alternative formulae for diabetic and non-diabetic subjects would defeat the primary purpose of the IVGTT - that of being a diagnostic test.

In the present study the use of mathematical methods has shown that in most cases no particular section of the IVGTT blood glucose slope is consistently and obviously better than any other for the calculation of the glucose disappearance rate. The same conclusion is reached for Cases 27 - 33, using blood sugar. Individual graphs indicate, however, that a calculation of k from best-fitting straight lines based on all valid points from the 20th minute onwards will usually represent the slope fairly closely. Hamilton and Stein (1942) found that in many cases the use of one point more or less made little difference to the values of k obtained. Ikkos and Luft (1957) also found that although a simple exponential relationship between blood sugar and time appeared to exist after the 25th minute from the time of glucose injection, this again was only a close approximation. Without further studies it is impossible to be sure whether these inexactitudes exist because an IVGTT blood glucose or blood sugar slope on semilogarithmic graph paper is actually a curve and not a straight line at all in any part, or whether they merely reflect the inevitable scatter of points on such a graph.

It is worth remembering again that conclusions based on blood "sugar" rather than blood glucose figures may be faulty and some at least of the discrepant views here discussed can perhaps be explained on these grounds.

"Total" or "Excess" blood glucose

On the question of whether to use "total" or "excess" blood glucose one can be more definite. Analysis of the individual and mean blood glucose values obtained in this series shows that even if all valid points are used in the calculation a better fit to a straight line is possible in the majority of cases when "total" blood glucose figures are used. If the first three valid points are omitted all cases show the superiority of "total" blood glucose. This is also shown in nearly all of cases 27 - 33, using blood sugar. Even for the two exceptions to this general finding in the present study the value for S_∞ which gives the minimum SE of points from the best-fitting straight line is appreciably less than S_f. These results, therefore, give no support whatever to the practice of using "excess" (over S_f) blood glucose or blood sugar for the calculation of k.

It can be shown (see pages 170 ff) that negative values of S_∞ will give an even smaller SE than $S_\infty = 0$. The larger the negative value of S_∞ the smaller will be the corresponding SE until SE = 0 when $S_\infty = -\infty$. These perfectly fitting blood glucose points would, of course, be in a horizontal line at a level of $+\infty$ and would be an absurdity for

any actual IVGTT. In practice, therefore, any possible values of S_∞ less than 0 need not be considered.

Simple Test.

Finally, to turn from theoretical considerations to practical procedures, it has been shown in the present study that use of only the 20, 40 and 60 minute blood glucose readings in an IVGTT provide nearly as much information as readings taken every 5 minutes. Values for k calculated by both methods differ only by an average of 5.7% ($\pm$ SD 4.3) if "total" blood glucose figures are used. It is suggested that for a test of this nature with so many possible variables a difference of this degree is well within acceptable confidence limits.

If "excess" blood glucose figures are used the values for k calculated by the two methods differ by an average of 6.6%. The Standard Deviation from this mean is $\pm$8.5. Both these figures are greater than those obtained with "total" blood glucose and it would appear, therefore, that use of "total" blood glucose provides more reliable and consistent results.

Distribution of k values

Sometimes the normal ranges have been expressed as the means and Standard Deviations for diabetics and non-diabetics (Baird and Duncan 1959). This device assumes that individual k values in these

two groups occur in a normal distribution and this is clearly not the case if a simple arithmetic scale is used. Figures XXXVIII and XXXIX show that diabetic k values tend to be crowded together at one end of the scale while non-diabetic values are scattered over a much wider range. It would seem that an arithmetic scale is not the ideal. A difference between two k values of, say, 0.4 is obviously more significant at the lower end of the scale than at the upper end and this proportional relationship would be much better expressed by some form of geometric or logarithmic scale. An example of such a scale is shown in Figure XLa and b where k ("total") values for the present series have been arranged as histograms. It will be seen that taking the group as a whole, k values fall very nearly into a normal unimodal distribution (Figure XLa). More surprisingly, perhaps, if diabetics and non-diabetics are considered separately they also form normal unimodal distributions of their k values (Figure XLb). A manipulation of the scale like this makes no difference, of course, to the actual ranges of k values obtained in a particular series but it does show more clearly their unbroken distribution from very low to very high, with a peak in the region of the "overlap" between the two groups. Such a scale also has the effect of drawing in the few anomalous k values nearer to the main ranges.

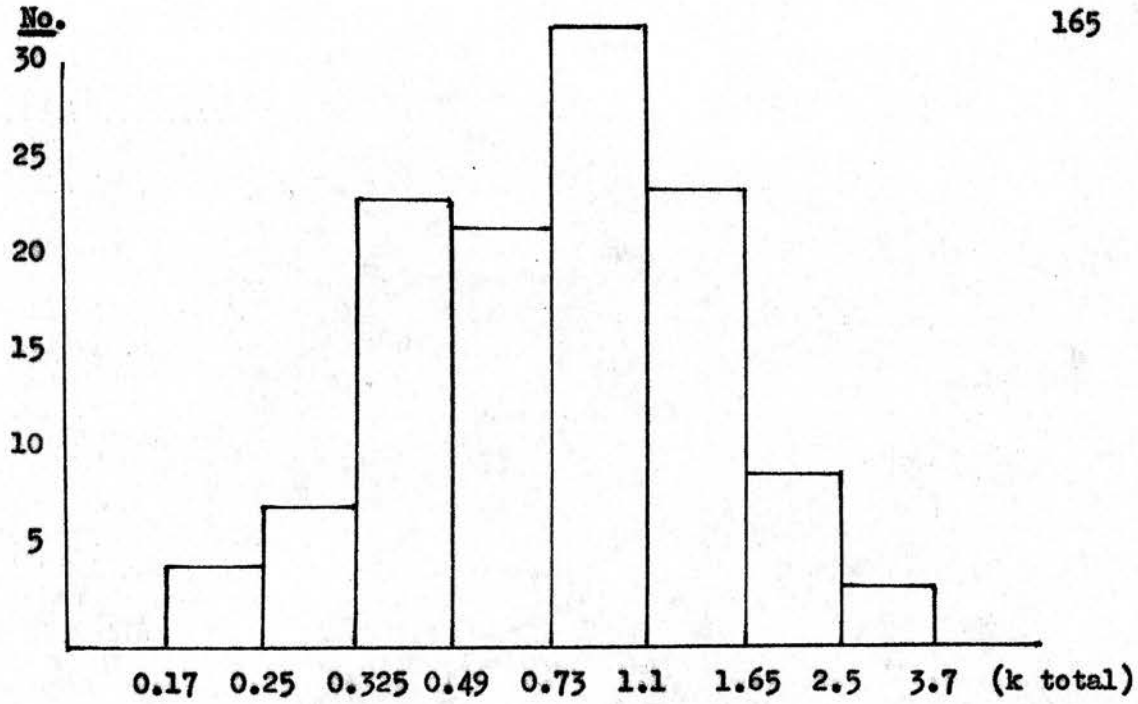


Figure XLa. Distribution histogram of k values - all subjects.

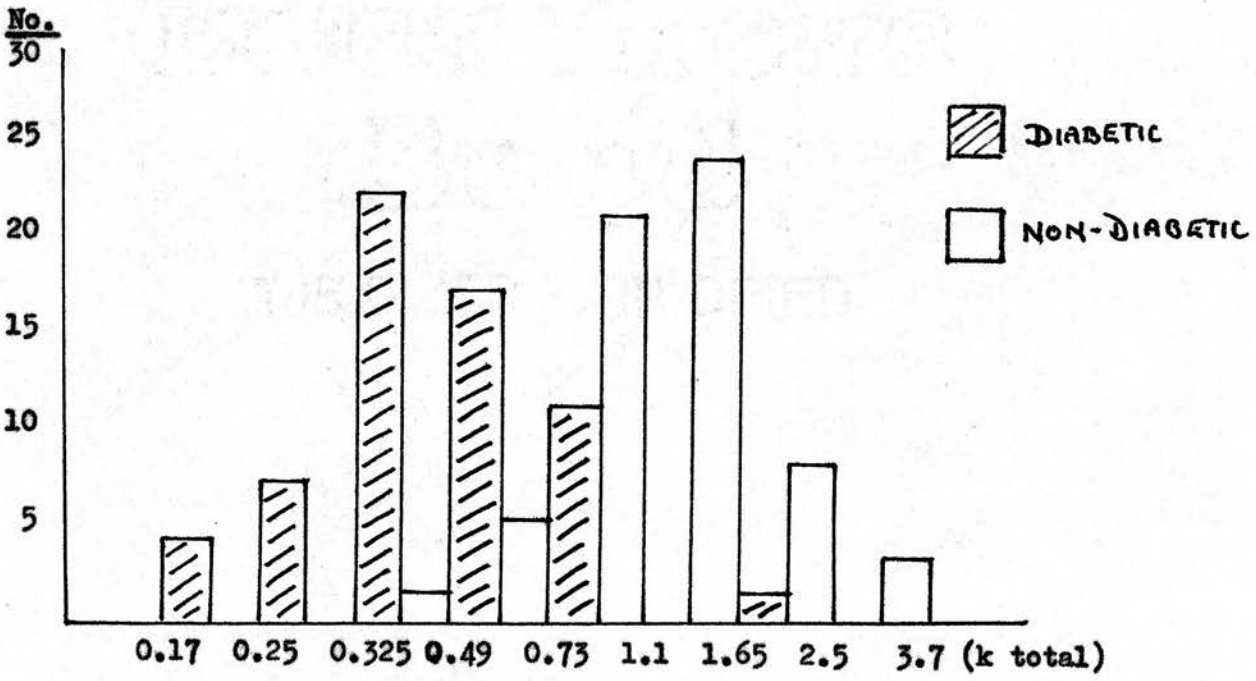


Figure XLb. Distribution histogram of k values - diabetics and non-diabetics separately

Anomalous results.

It is, perhaps, inevitable that when testing a physiological process such as glucose disappearance from the blood a few apparently anomalous results (in this context, k values well outside the main ranges) will occur. No satisfactory explanation can be offered. Differences in the methods of blood collection and blood sugar and blood glucose estimation in the OGTT and the IVGTT do not appear adequate by themselves to account for their occurrence: all the individuals with such results in the diabetic group were true diabetics by any reasonable definition, although it is less easy to be so sure about the non-diabetics.

One weakness of the test as reported here is the large number of results which fall into the overlapping sections of the two ranges. Lundbaek (1962) reported only a very small overlap in his series while Amatuzio et al. (1953) found a clear separation. In view of the apparently unbroken spectrum of "diabeticity" in a large population it is difficult to see how there can be such an obvious distinction between diabetics and non-diabetics as these authors claim - some overlap is almost inevitable. When, however, as here, - using k ("total") - it includes over a quarter of the total number (39 cases: 21 diabetics and 18 non-diabetics) the technique or the interpretation of the test may need further scrutiny. Why should some "OGTT diabetics" have such high k values? Alternatively, why should some "OGTT non-diabetics" have such low k values? It does not appear that increasing the number of blood glucose readings from 3

to 11 would make any material difference. Of the 13 cases whose k values fell into the "overlap" range and who also had the longer (11 point) test none would move upwards or downwards clearly out of it if k ("total") values based on the longer test were substituted (see cases 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 17, 22 and 23 in Table VII).

A number of points may be mentioned. One reason why a diabetic patient might have a higher than expected k value would be the continuing effect of previously administered antidiabetic drugs. This might be the case in 14 subjects in the present series who were receiving chlorpropamide up to 48 hours before the test. Of these 14 patients 8 had k values within the "over-lap". However, even if these 8 individuals are excluded from the analysis the overlap range (using k ("total")) remains the same, namely 0.60 - 1.01, embracing 13 diabetics and 18 non-diabetics.

Another possible reason for the high k values of the diabetics in the "overlap" might be that they were all very mild diabetics. There were, in fact, 6 very mild diabetics (that is, controlled on diet alone) in the overlap section and one well above it. On the other hand, there were 9 similarly mild diabetics well below the overlap, with small k values. Furthermore, the "overlap" group also included 4 patients who required insulin for adequate control and could therefore be regarded as at least moderately severe diabetics.

It is said that diabetic-like abnormalities may be found in non-diabetics as a result of prolonged bed rest (Loeb and Stadler 1914,

Blotner 1945). In the overlap section 8 non-diabetics were bed-fast. However, 6 other non-diabetics who were also bed-fast had k values above the "overlap", (in the case of 3 individuals, only just above it). 5 bed-fast diabetics (one requiring insulin) also had k values in or above the overlap.

The age structure of the subjects studied may have a significant influence on the ranges of k values obtained. In this series it must be admitted that the two groups were not matched for age, the average age for all diabetics being 63.7 years and for all non-diabetics 50.9 years. However, one might expect the lower average age of the non-diabetics to have made a clearer separation between the two groups than would have been likely if the groups had been matched. In other words, any overlap would be reduced and not increased. As a matter of fact the average ages respectively of diabetics and non-diabetics in the overlap section are much closer than for the two groups taken altogether, being 65.4 years for diabetics and 59.3 years for non-diabetics. Furthermore the non-diabetics include in their number three individuals of 30 years old or less. If these three are excluded, the average age of the remainder is almost the same as for the diabetics, namely 66.4 years. This, of course, makes the position of these three young subjects even more anomalous.

It seems clear, in fact, that our main concern should be the "non-diabetics" with low k values rather than the diabetics with high

values who were, as already stated, true diabetics by any reasonable definition. These non-diabetics, in common with all other subjects tested were classified as such on the results of OGTT's. 14 of these 18 subjects in the "overlap" had OGTT blood sugars well below the levels taken as the upper limits of normal at the various stages of that test. The 2-hour blood sugar levels in the remaining 4 (cases 93, 94, 111 and 114) were borderline. None had symptoms referable to possible underlying diabetes and none had any family history of the disease. However, 5 other individuals (cases 92, 112, 116, 125 and 131) also had similar borderline 2-hour OGTT blood sugar levels but k values above the overlap range.

It is known that glucose tolerance is less when glucose is given intravenously than when it is taken orally (p.71). The 18 individuals with normal OGTT results but IVGTT k values in the "overlap" may therefore very possibly be those who, while not as yet showing OGTT abnormality, are on the verge of diabetes. They might thus show diabetic responses to the slightly more severe strain of an IVGTT.

It is, of course, just this group with equivocal GTT results which is of most interest to workers in this field. The implication of any given result in such cases can only be known after prolonged follow up of large numbers. Longitudinal studies of this type have only recently been undertaken and may eventually provide satisfactory answers to the problem. For the time being, therefore, it is suggested that all OGTT non-diabetics in the "overlap" section of an

IVGTT series such as this should be classed as diabetic "suspects".

As explained, there may be any one of a number of possible reasons (such as prolonged bed rest, chronic illness, old age or obesity) for a low k value in a particular individual. Nevertheless, as the same factors can also be present in other individuals without necessarily producing equally low k values, the term "diabetic suspect" for the former seems appropriate.

It is possible that valuable prognostic information could be obtained in such individuals (as also in those mentioned above with anomalous k values well outside the main ranges) by a study of insulin levels during an IVGTT or by the use of one or other of the "provocative" GTT's described earlier. Follow up of this group would be necessary to discover how many of them actually develop florid diabetes but present evidence suggests that many will. Meanwhile the existence of these non-diabetics with k values within the diabetic range does not invalidate the general assertion that the IVGTT is to be preferred to the OGTT as an accurate indicator of carbohydrate metabolism.

Mathematical Note

It has been shown in Figure IV that within the range +300 to -300 the further a series of points deviates (in either direction) from points lying in a straight line on semilogarithmic graph paper, the greater is the scatter from best-fitting straight lines passing through them. In this Figure line A-A represents a simple exponential

relationship between blood glucose and time of the form:-

$$\log (S - S_\infty) = \log (S_0 - S_\infty) - kt, \text{ when } S_\infty = 0.$$

Lines B-B, B'-B' and B"-B" represent similar relationships when S_∞ is respectively -100, -200 and -300, while lines C-C, C'-C' and C"-C" represent further series derived from points lying along A-A when S_∞ is respectively +100, +200 and +300.

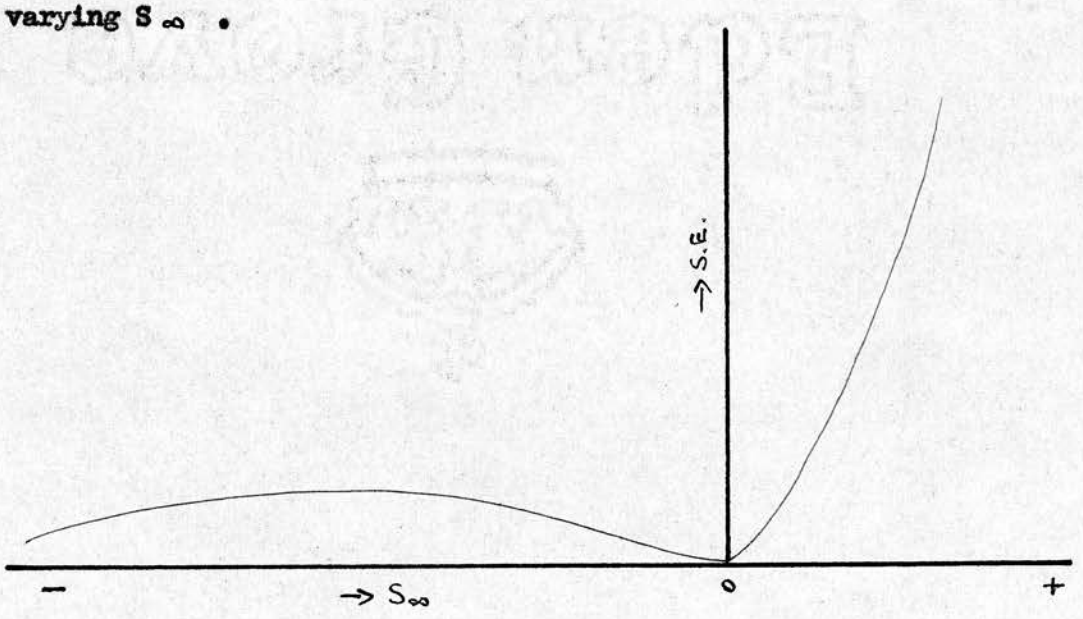
S	SE
+300	6.21
+200	1.65
+100	0.46
0	0.00
-100	0.21
-200	0.30
-300	0.34
-400	0.36
-500	0.36
-600	0.36
-700	0.35
-800	0.34
-900	0.33
-1000	0.32

Table X.

SE from best-fitting straight lines of points derived from A-A in Figure IV, for varying values of S_∞.

Clearly the maximum possible <u>positive</u> value for S_∞ will be somewhere between S_o and the value of S when t = 60, depending on how many blood glucose points are required for the calculation of k. On the <u>negative</u> side, however, there is no limit, and any value of S_∞ up to $-\infty$ may be used. It can be shown that for a perfect straight line series (such as A-A) an increasing negative value for S_∞ will produce first an increase in the scatter of points from a straight line, that is, an increasing SE, and then, after reaching a maximum, a progressive diminution in SE until SE = 0 when $S_\infty = -\infty$.

Table X gives the SE from best-fitting straight lines of points derived from A-A in Figure IV, for different values of S_∞, and Figure XLI illustrates graphically the distribution of the same SE values with varying S_∞.



<u>Figure XLI.</u> Distribution graph of SE for varying S_∞ derived from a straight line series of points.

Table XI shows the SE from best-fitting straight lines of points derived from three actual IVGTT results in the present series (cases, 3, 22 and 26) for different values S_∞ . Only negative values of S_∞ are shown. Alterations of SE for different positive values of S_∞ may be seen in Tables IV and V: in all, increasing S_∞ produces an increase in SE. In Table XI all valid points have been used for the calculation in the case of No. 22, while the first three valid points in each case have been omitted from the calculation in Nos. 3 and 26. Figure XLII illustrates the approximate distribution graph of SE for varying S_∞ for any one of these three cases. In this figure both positive and negative values of S_∞ have been incorporated.

From Tables IV, V, XI and Figure XLII it will be seen that the minimum value for SE is when $S_\infty = -\infty$. On the other hand, Table X and Figure XLI (for a perfect straight line and figures derived from it) show two minima, one when $S_\infty = 0$ and the other when $S_\infty = -\infty$. Thus the graphs of SE against S_∞ derived respectively from hypothetical and actual IVGTT's are essentially different.

There are two possible interpretations of these findings. The first is that they may simply reflect the scatter of points on an actual IVGTT graph compared with the perfect straight line series in the imaginary test represented by A-A in Figure IV. Increasing negative values of S_∞ (that is, the addition of increasingly large numbers to the observed blood glucose readings) would progressively

No. 22, points 1-11		Nos.3, points 4-11		No. 26, points 4-10	
S_∞	SE	S_∞	SE	S_∞	SE
0	2.11	0	1.03	0	1.04
-10	2.08	-10	0.97	-10	0.93
-20	2.04	-20	0.96	-20	0.83
-30	2.00	-30	0.93	-30	0.75
-40	1.97	-40	0.90	-40	0.68
-50	1.94	-50	0.87	-50	0.62
-60	1.90	-60	0.85	-60	0.57
-70	1.87	-70	0.82	-70	0.52
-80	1.84	-80	0.80	-80	0.48
-90	1.81	-90	0.78	-90	0.45
-100	1.78	-100	0.76	-100	0.42
-200	1.52	-200	0.60	-200	0.25
-300	1.32	-300	0.50	-300	0.18
-400	1.16	-400	0.42	-400	0.14
...	...	-500	0.37	-500	0.12
...	...	-600	0.33	-600	0.11
...	...	-700	0.29	-700	0.10
...	...	-800	0.27	-800	0.09
...	...	-900	0.24	-900	0.08
-1000	0.68	-1000	0.22	-1000	0.07
-5000	0.18	...	...	...	...

Table XI. SE from best-fitting straight lines of points derived from actual IVGTT graphs (cases 3, 22 and 26) for varying values of S_∞ .

smooth out any irregularities until a perfect straight line is obtained when $S_\infty = -\infty$.

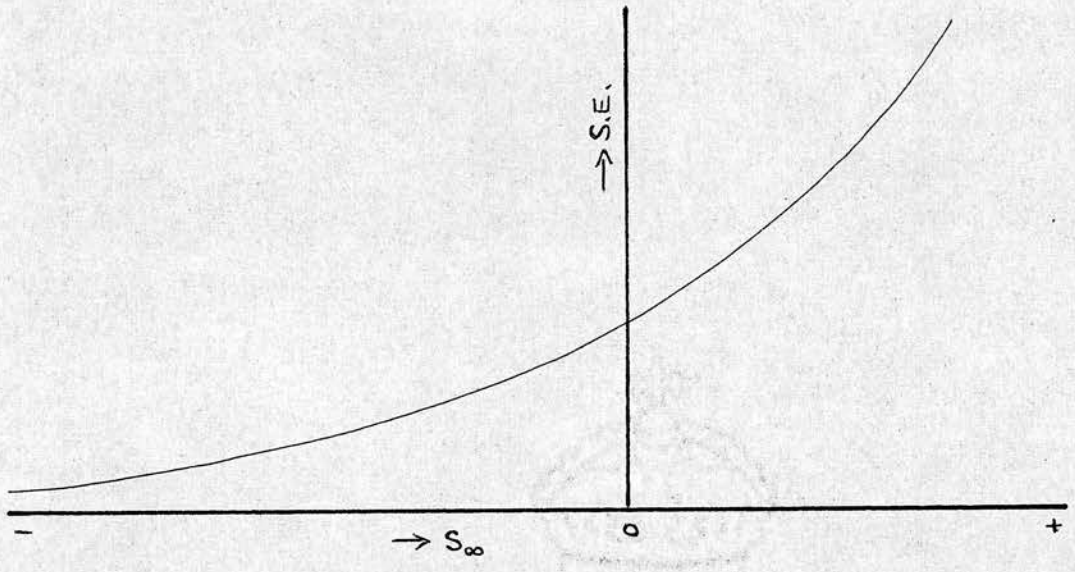


Figure XLII. Approximate distribution graph of SE for varying S_∞ derived from actual IVGTT graphs (Cases 3, 22 and 26).

An alternative explanation, however, is that there is no straight line section on a semilogarithmic IVGTT graph. That is, that there is no simple exponential relationship between blood glucose and the time after glucose injection in an IVGTT. Perhaps a more complex relationship should be sought.

While, therefore, use of the IVGTT on the assumption that it represents a simple exponential relationship is convenient in practice, it is suggested that the ideal interpretation has yet to be devised. More study, perhaps along the mathematical lines discussed above, is required before a fully satisfactory answer can be found.

CONCLUSIONS

1. In the interpretation of the IVGTT, "total" blood glucose figures should be used rather than "excess" blood glucose.

2. No definite conclusions may be drawn from this study as to the most appropriate section of the blood glucose curve to be used in the interpretation of an IVGTT. A straight line fitted to all points between the 20th minute after glucose injection and the last point before the blood glucose falls to within 25 mg per 100 ml of the original fasting figure will represent the results of most IVGTT's reasonably accurately. The inclusion of one or two points on either side of this section will, however, usually make little difference.

3. There are physiological and mathematical grounds for suggesting that no simple exponential relationship between blood glucose and time after glucose injection exists at any time during an IVGTT. The assumption of such a relationship is, however, convenient in practice and serves very well for ordinary purposes.

4. Use of blood glucose readings taken at 20, 40 and 60 minutes after glucose injection will provide a result nearly as accurate as a test involving readings at five-minute intervals. This simpler test is recommended as a satisfactory substitute for everyday use.

5. With this technique the main ranges of k ("total") values in this series were:- Diabetics, 0.20 to 1.01

Non-diabetics, 0.60 to 2.74

It is suggested that those individuals with k values below 1.01 who are not already diabetic be termed diabetic "suspects".

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APPENDIX

Individual case summaries and details of glucose tolerance tests

Notes (a) Blood sugar and blood glucose values are expressed in mg per 100 ml. to the nearest milligramme. (For detailed technique see pages 88-91).

(b) Urine sugar was estimated by Clinitest tablets and is recorded simply as 0, Trace, +, ++, +++ or ++++.

(c) Times are recorded in hours (after oral glucose) for OGTT's and minutes (after the mid-point of glucose injection) for IVGTT's. F = Fasting.

(d) Blood glucose, k and SE for IVGTT's are recorded for both "total" - T - and "excess" (over S_f) - E - values.

(e) As the blood glucose falls during an IVGTT, k values are negative. For convenience, however, they are all here recorded as positive.

(f) All k and SE values are multiplied by 100.

(g) Blood glucose levels less than 25 mg per 100 ml in excess of S_f are included in brackets.

(h) Subjects are graded either obese, average or thin and as either ambulant or non-ambulant.

1. M.W. Male. 67 yrs. Obese. Ambulant.

Known diabetic for two years. Treated with oral antidiabetic drugs and diet only.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	122	-
		5	344	222
		10	311	189
		15	300	178
		20	278	156
		25	267	145
		30	244	122
		35	239	117
		40	233	111
		45	228	106
		50	222	100
		60	217	95
Using all valid points		k	0.85	1.59
		SE	4.39	6.86
Using points 4 - 11		k	0.62	1.25
		SE	2.84	5.08
Using 20, 40, 60 minute points		k	0.62	1.25
		SE	4.11	7.15

2. E.McD. Female. 67 yrs. Obese. Ambulant.

Osteo-arthritis of both knees. Known diabetic for 6 years.

Treated with diet and oral antidiabetic drugs.

	Time		Blood glucose	
			T	E
OGTT not done	IVGTT	F	100	-
		5	240	140
		10	230	130
		15	220	120
		20	205	105
		25	190	90
		30	185	85
		35	180	80
		40	175	75
		45	170	70
		50	160	60
		60	150	50
Using all valid points		k	0.86	1.74
		SE	2.26	3.48
Using points 4 - 11		k	0.73	1.72
		SE	1.44	3.52
Using 20,40, 60 minute points		k	0.78	1.85
		SE	0.18	2.82

3. A.D. Female. 58 yrs. Obese. Ambulant.

Known diabetic for 9 years. Father and one sister also have diabetes. Admitted for investigation of epigastric pain. No definite cause found. Treated with diet and oral antidiabetic drugs.

	Time	Blood glucose	
		T	E
OGTT not done	IVGTT F	100	-
	5	280	180
	10	260	160
	15	250	150
	20	240	140
	25	230	130
	30	220	120
	35	210	110
	40	200	100
	45	190	90
	50	180	80
	60	170	70
Using all valid points	k	0.91	1.72
	SE	1.10	2.17
Using points 4 - 11	k	0.90	1.80
	SE	1.03	1.82
Using 20, 40, 60 minute points	k	0.86	1.73
	SE	0.81	0.82

4. H.H. Female. 58 yrs. Obese. Ambulant.

Known diabetic for 4 years. No family history of diabetes.

Requires insulin for adequate control but not liable to ketosis.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	263	-
		5	450	187
		10	388	125
		15	375	112
		20	363	100
		25	350	87
		30	338	75
		35	325	62
		40	313	50
		45	300	37
		50	288	25
		(60	275	12)
Using all valid points		k	0.86	3.90
		SE	3.07	12.10
Using points 4 - 10		k	0.77	4.47
		SE	0.31	10.59
Using 20, 40 minute points		k	0.74	3.47
		SE	-	-

5. M.B. Female. 66 yrs. Obese. Ambulant.

Known diabetic for 3 years. Admitted for re-stabilisation.

Requires insulin for adequate control but not liable to ketosis.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	200	-
		5	400	200
		10	390	190
		15	380	180
		20	370	170
		25	360	160
		30	350	150
		35	340	140
		40	320	120
		45	300	100
		50	290	90
		60	260	60
Using all valid points		k	0.77	2.05
		SE	2.52	10.59
Using points 4 - 11		k	0.90	2.58
		SE	1.78	8.05
Using 20,40 60 minute points		k	0.88	2.60
		SE	2.55	14.08

6. G.McR. Male. 61 yrs. Obese. Non-ambulant.

Admitted with popliteal artery embolism following an attack of paroxysmal supraventricular tachycardia. OGTT showed mild diabetes. Treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	86	0	IVGTT	F	94	-
	1	210	0		5	329	235
	2	140	0		10	306	212
					15	282	188
					20	247	153
					25	241	147
					30	235	141
					35	223	129
					40	212	118
					45	200	106
					50	184	90
					60	171.	77
Using all valid points					k	1.17	1.98
					SE	3.33	4.50
Using points 4 - 11					k	0.99	1.82
					SE	2.12	4.59
Using 20,40,60 minute points					k	0.92	1.73
					SE	2.53	6.84

7. W.W. Male 77 yrs. Average. Ambulant.

Known diabetic for 14 years. Treated with diet and oral anti-diabetic drugs. Admitted for investigation of hepato-splenomegaly. No definite cause found.

		Time	Blood glucose	
OGTT not done			T	E
	IVGTT	F	106	-
		5	318	212
		10	305	199
		15	294	188
		20	269	163
		25	259	153
		30	247	141
		35	247	141
		40	235	129
		45	223	117
		50	218	112
		60	200	94
Using all valid points		k	0.83	1.45
		SE	1.92	2.79
Using points 4 - 11		k	0.73	1.34
		SE	1.23	2.62
Using 20, 40, 60 minute points		k	0.74	1.38
		SE	1.11	3.46

8. C.F. Male. 59 yrs. Average. Ambulant.

Admitted for investigation of intermittent claudication. Found to have left femoral artery thrombosis. Diabetes found on routine testing. Treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	152	0	IVGTT	F	119	-
	1	296	Trace		5	362	243
	2	200	+++		10	325	206
					15	281	162
					20	275	156
					25	269	150
					30	262	143
					35	250	131
					40	237	118
					45	231	112
					50	225	106
					60	206	87
Using all valid points					k	0.91	1.66
					SE	4.58	6.57
Using points 4 - 11					k	0.74	1.47
					SE	1.01	2.42
Using 20,40,60 minute points					k	0.72	1.45
					SE	0.24	1.25

9. D.McA. Male. 74 yrs. Average. Ambulant.

Known diabetic for 4 years. Controlled with diet and oral anti-diabetic drugs.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	88	-
		5	288	200
		10	275	187
		15	269	181
		20	263	175
		25	257	169
		30	250	162
		35	244	156
		40	238	150
		45	225	137
		50	212	124
		60	200	112
Using all valid points		k	0.63	1.00
		SE	1.70	3.15
Using points 4 - 11		k	0.70	1.14
		SE	1.58	2.83
Using 20, 40, 60 minute points		k	0.68	1.10
		SE	2.93	5.45

10. P.B. Male. 66 yrs. Average. Non-ambulant.

Admitted for investigation of weight loss. Diabetes found on routine testing. Requires insulin for adequate control but not liable to ketosis.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	143	0	IVGTT	F	171	-
	1	252	0		5	428	257
	2	273	++		10	371	200
					15	357	186
					20	343	172
					25	314	143
					30	300	129
					35	293	122
					40	285	114
					45	278	107
					50	271	100
					60	257	86
	Using all valid points				k	0.86	1.88
					SE	4.43	6.82
	Using points 4 - 11				k	0.65	1.58
					SE	2.33	4.25
	Using 20, 40, 60 minute points				k	0.72	1.73
					SE	3.14	4.81

11. A.M. Male. 51 yrs. Thin. Ambulant.

Admitted for manipulation of right shoulder for osteoarthritis. Known diabetic for 16 years. Requires insulin for adequate control but not liable to ketosis.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	260	-
		5	400	140
		10	390	130
		15	385	125
		20	380	120
		25	375	115
		30	360	100
		35	360	100
		40	350	90
		45	340	80
		50	325	65
		60	320	60
Using all valid points		k	0.42	1.58
		SE	1.19	6.17
Using points 4 - 11		k	0.46	1.86
		SE	1.23	5.42
Using 20, 40, 60 minute points		k	0.43	1.73
		SE	0.30	4.81

12. E.B. Female. 58 yrs. Thin. Ambulant.

Admitted with a history of polyuria and thirst for three weeks. Heavy glycosuria but no ketosis. Requires insulin for control.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	299	++++	IVGTT	F	192	-
	1	440	++++		5	346	154
	2	528	++++		10	331	139
					15	323	131
					20	308	116
					25	292	100
					30	284	92
					35	277	85
					40	269	77
					45	261	69
					50	254	62
					60	246	54
Using all valid points					k	0.64	1.97
					SE	1.66	2.32
Using points 4 - 11					k	0.55	1.90
					SE	1.14	2.16
Using 20, 40, 60 minute points					k	0.56	1.91
					SE	1.79	1.99

13. H.D. Male. 46 yrs. Obese. Ambulant.

Admitted for investigation of "panic" attacks. No organic cause found. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	102	0	IVGTT	F	88	-
	1	176	0		5	311	223
	2	80	0		10	235	147
					15	223	135
					20	200	112
					25	188	100
					30	176	88
					35	164	76
					40	153	65
					45	141	53
					50	117	29
					(60	94	6)
Using all valid points					k	1.81	3.68
					SE	6.15	14.59
Using points 4 - 10					k	1.65	4.00
					SE	4.05	16.10
Using 20, 40 minute points					k	1.34	2.73
					SE	-	-

14. A.B. Male. 57 yrs. Average. Ambulant.

Admitted for investigation of "palpitations". No abnormality found.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	106	0	IVGTT	F	94	-
	1	170	0		5	219	125
	2	107	0		10	212	118
					15	200	106
					20	187	93
					25	175	81
					30	162	68
					35	150	56
					40	137	43
					45	131	37
					50	125	31
					(60	112	18)
Using all valid points					k	1.34	3.24
					SE	1.79	7.58
Using points 4 - 10					k	1.40	3.78
					SE	1.51	3.02
Using 20, 40 minute points					k	1.55	3.81
					SE	-	-

15. M.B. Male. 57 yrs. Average. Ambulant.

Admitted following the thrombosis of the superior mesenteric artery. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	84	0	IVGTT	F	105	-
	1	122	0		5	428	323
	2	108	0		10	380	275
					15	370	265
					20	353	246
					25	307	202
					30	300	195
					35	285	180
					40	280	175
					45	275	170
					50	250	145
					60	235	130
	Using all valid points				k	1.05	1.60
					SE	3.84	5.00
	Using points 4 - 11				k	0.91	1.45
					SE	3.38	4.95
	Using 20, 40, 60 minute points				k	1.02	1.61
					SE	2.31	2.10

16. D.T. Male. 23 yrs. Average. Ambulant.

Healthy medical student. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	94	0	IVGTT	F	85	-
	1	155	0		5	270	185
	2	102	0		10	260	175
					15	250	165
					22	220	135
					26	210	125
					30	200	115
					35	190	105
					40	170	85
					45	150	65
					50	145	60
					60	125	40
Using all valid points					k	1.46	2.80
					SE	2.89	9.28
Using points 4 - 11					k	1.56	3.27
					SE	2.52	6.49
Using 22, 40, 60 minute points					k	1.49	3.21
					SE	0.81	9.27

17. R.W. Male. 77 yrs. Average. Ambulant.

Glycosuria found on routine testing by General Practitioner. No other evidence for or family history of diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	95	0	IVGTT	F	82	-
	1	174	0		5	263	181
	2	77	0		10	236	154
					15	227	145
					20	218	136
					25	200	118
					30	191	109
					35	182	100
					40	163	81
					45	159	77
					50	154	72
					60	150	68
	Using all valid points				k	1.08	1.90
					SE	3.66	5.48
	Using points 4 - 11				k	0.98	1.83
					SE	3.80	6.38
	Using 20, 40, 60 minute points				k	0.93	1.73
					SE	8.18	13.41

18. J.S. Male. 68 yrs. Average. Ambulant.

Admitted for investigation of intermittent claudication. Found to have bilateral common iliac artery thrombosis. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	100	0	IVGTT	F	81	-
	1	122	0		5	250	169
	2	80	0		10	237	156
					15	225	144
					20	212	131
					25	200	119
					30	187	106
					35	175	94
					40	162	81
					45	150	69
					50	137	56
					60	125	44
	Using all valid points				k	1.31	2.48
					SE	1.69	6.29
	Using points 4 - 11.				k	1.38	2.83
					SE	1.41	3.74
	Using 20, 40, 60 minute points				k	1.33	2.74
					SE	0.24	5.63

19. J.G. Male. 62 yrs. Average. Ambulant.

Admitted for investigation of intermittent claudication. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	100	0	IVGTT	F	88	-
	1	152	0		5	313	225
	2	92	0		10	263	175
					15	250	162
					20	213	125
					25	200	112
					30	188	100
					35	175	87
					40	163	75
					45	150	62
					50	138	50
					60	125	37
Using all valid points					k	1.62	3.15
					SE	4.30	4.50
Using points 4 - 11					k	1.38	3.10
					SE	1.41	4.54
Using 20, 40, 60 minute points					k	1.33	3.01
					SE	0.24	7.44

20. B.W. Female. 40 yrs. Average. Ambulant.

Healthy doctor. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	76	0	IVGTT	F	85	-
	1	134	0		5	270	185
	2	80	0		10	245	160
					15	200	115
					20	190	105
					28.5	185	100
					30.5	160	75
					35	140	55
					40	120	35
					45	80	-5
					50	60	-25
					60	50	-35
Using all valid points					k	2.13	4.23
					SE	6.55	17.23
Using points 4 - 8					k	2.42	5.64
					SE	7.44	19.20
Using 20, 40 minute points					k	2.30	5.49
					SE	-	-

21. L.L. Female. 25 yrs. Average. Ambulant.

Healthy laboratory technician. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose.	
		Blood	Urine			T	E
OGTT	F	97	0	IVGTT	F	85	-
	1	142	0		5	254	169
	2	100	0		10	239	154
					15	185	100
					21.5	173	88
					25.5	154	69
					30	146	61
					35.5	139	54
					40	116	31
					45	112	27
					50	108	23
					60	93	8
	Using all valid points				k	2.08	4.59
					SE	5.38	11.94
	Using points 4 - 9				k	1.86	5.10
					SE	3.88	12.57
	Using 21.5, 40 minute points				k	2.19	5.70
					SE	-	-

22. P.R. Male. 65 yrs. Thin. Ambulant.

Admitted for investigation of weight loss. No definite cause found.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	94	0	IVGTT	F	113	-
	1	170	++		5	375	262
	2	77	+		10	338	225
					15	325	212
					20	306	193
					25	300	187
					30	275	162
					35	263	150
					40	250	137
					45	237	124
					50	225	112
					60	213	100
Using all valid points					k	1.03	1.75
					SE	2.11	2.64
Using points 4 - 11					k	0.98	1.76
					SE	1.81	2.58
Using 20, 40, 60 minute points					k	0.91	1.65
					SE	1.64	0.99

23. M.E. Male. 59 yrs. Thin. Ambulant.

Admitted for investigation of intermittent claudication. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	86	0	IVGTT	F	60	-
	1	140	0		5	250	190
	2	61	0		10	230	170
					15	210	150
					20	205	145
					25	195	135
					30	190	130
					35	185	125
					40	170	110
					45	165	105
					50	155	95
					60	150	90
Using all valid points					k	0.91	1.28
					SE	2.75	3.53
Using points 4 - 11					k	0.83	1.28
					SE	2.00	2.99
Using 20, 40, 60 minute points					k	0.78	1.19
					SE	2.53	3.09

24. B.M. Male. 22 yrs. Thin. Ambulant.

Admitted for investigation of persistent diarrhoea. No organic cause found. No previous evidence for or family history of any diabetic tendency.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	106	0	IVGTT	F	75	-
	1	170	0		5	287	212
	2	90	0		10	250	175
					15	212	137
					20	175	100
					25	168	93
					30	150	75
					35	137	62
					40	125	50
					45	119	44
					50	112	37
					(60	85	10)
Using all valid points					k	2.08	3.88
					SE	6.31	5.73
Using points 4 - 10					k	1.58	3.48
					SE	2.38	4.15
Using 20, 40 minute points					k	1.68	3.47
					SE	-	-

25. Present series. Mean blood glucose values, k. and SE for twelve diabetic patients.

	Time	Blood glucose	
		T	E
	F	156	-
	5	350	194
	10	326	170
	15	312	156
	20	299	143
	25	287	131
	30	276	120
	35	269	113
	40	259	103
	45	250	94
	50	240	84
	60	227	71
Using all valid points	k	0.76	1.77
	SE	1.49	1.62
Using points 4 - 11.	k	0.69	1.75
	SE	0.53	1.34
Using 20, 40, 60 minute points	k	0.74	1.93
	SE	0.47	4.87

26. Present series. Mean blood glucose values, k and SE for twelve non-diabetic patients.

	Time	Blood glucose	
		T	E
	F	104	-
	5	285	181
	10	255	151
	15	233	129
	20	211	107
	25	197	93
	30	183	79
	35	171	67
	40	156	52
	45	144	40
	50	132	28
	(60	115	11)
Using all valid points	k	1.65	3.89
	SE	1.53	9.04
Using points 4 - 10	k	1.57	4.37
	SE	1.04	8.99
Using 20, 40 minute points	k	1.50	3.57
	SE	-	-

27. Mean blood sugar values, k and SE for six non-diabetic patients from data reported by Greville (1943).

	Time	Blood sugar	
		T	E
	F	89	-
	5	287	198
	10	247	158
	20	199	110
	30	172	83
	35	159	70
	40	147	58
	45	139	50
	50	125	36
	55	117	28
	(60	111	22)
Using all valid points	k	1.72	3.46
	SE	3.36	5.55
Using points 3 - 9	k	1.52	3.85
	SE	0.83	5.77
Using 20, 40 minute points	k	1.51	3.18
	SE	-	-

28. Mean blood sugar values, k and SE for twenty six diabetic patients from data reported by Amatuzio et al. (1953).

	Time	Blood sugar	
		T	E
	F	115	-
	4	271	156
	12	245	130
	20	227	112
	28	213	98
	36	201	86
	44	192	77
	52	182	67
	60	171	56
Using all valid points	k	0.78	1.75
	SE	1.97	2.29
Using points 3 - 8	k	0.69	1.88
	SE	0.53	2.25
Using 20, 44, 60 minute points	k	0.71	1.72
	SE	0.20	3.34

29. Mean blood sugar values, k and SE for seventy non-diabetic patients from data reported by Amatuzio et al. (1953).

	Time	Blood sugar	
		T	E
	F	94	-
	4	267	173
	12	221	127
	20	192	98
	28	171	77
	36	153	59
	44	139	45
	52	127	33
	(60	113	19)
Using all valid points	k	1.51	3.37
	SE	3.70	2.19
Using points 3 - 7	k	1.29	3.38
	SE	1.03	1.65
Using 20, 44 minute points	k	1.35	3.24
	SE	-	-

30. Mean blood sugar values, k and SE for fifteen diabetic patients from data reported by Duncan (1956_a).

	Time	Blood sugar	
		T	E
	F	169	-
	5.5	388	219
	15.5	338	169
	20.5	322	153
	25.5	309	140
	30.5	297	128
	35.5	284	115
	45.5	266	97
	55.5	245	76
	65.5	237	68
Using all valid points	k	0.80	1.93
	SE	2.78	3.19
Using points 3 - 9	k	0.70	1.90
	SE	1.39	2.92
Using 20.5, 35.5, 55.5 minute points	k	0.68	1.79
	SE	1.73	0.59

31. Mean blood sugar values, k and SE for twenty non-diabetic patients from data reported by Duncan (1956a).

	Time	Blood sugar T	Blood sugar E
	F	96	-
	5.5	296	200
	15.5	234	138
	20.5	203	107
	25.5	186	90
	30.5	172	76
	35.5	159	63
	45.5	132	36
	55.5	125	29
	(65.5	113	17)
Using all valid points	k	1.69	3.80
	SE	5.35	2.67
Using points 3 - 8	k	1.38	3.83
	SE	1.52	2.57
Using 20.5, 35.5, 55.5 minute points	k	1.39	3.75
	SE	2.68	3.20

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32. Mean blood sugar values, k and SE for diabetic patients from data reported by Ikkos and Luft (1957).

	Time	Blood sugar	
		T	E
	F	212	-
	10	370	158
	15	355	143
	20	345	133
	25	339	127
	30	335	123
	35	329	117
	40	321	109
	45	318	106
	50	313	101
	55	308	96
	60	304	92
Using all valid points	k	0.37	1.02
	SE	1.03	2.05
Using points 3 - 11	k	0.32	0.94
	SE	0.32	0.89
Using 20, 40, 60 minute points	k	0.32	0.92
	SE	0.72	1.20

33. Mean blood sugar values, k and SE for sixteen non-diabetic patients from data reported by Ikkos and Luft (1957).

	Time	Blood sugar	
		T	E
	F	72	-
	10	229	157
	15	211	139
	20	194	122
	25	177	105
	30	164	92
	35	151	79
	40	141	69
	45	131	59
	50	124	52
	55	114	42
	60	106	34
Using all valid points	k	1.53	3.02
	SE	1.30	4.04
Using points 3 - 11	k	1.48	2.95
	SE	1.00	3.66
Using 20, 40, 60 minute points	k	1.51	3.19
	SE	1.38	5.63

34. M.O'C. Male. 54 yrs. Obese. Ambulant.

Admitted for cholecystectomy (chronic cholecystitis). Glycosuria noticed on two or three occasions in the previous few years but no treatment given. Controlled with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	128	0	IVGTT	F	65	-
	1	220	*		20	133	68
	2	205	+++		40	122	57
					60	100	35
				k		0.72	1.67

35. J.D. Male. 55 yrs. Obese. Ambulant.

Admitted following severe epistaxis. Known hypertensive. GTT done routinely. Treated subsequently with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	144	0	IVGTT	F	112	-
	1	236	0		20	212	100
	2	156	0		40	187	75
					60	175	63
				k		0.48	1.16

36. M.W. Male. 63 yrs. Obese. Ambulant.

Admitted with herpes zoster ophthalmicus. Glycosuria noted on routine urine testing. Treated with oral antidiabetic drugs and diet.

OGTT not done

Fasting blood sugar on admission, 260 mg/100 ml.

	Time	Blood glucose	
		T	E
IVGTT	F	257	-
	20	414	157
	42	371	114
	61	342	85
k		0.46	1.48

37. R.D. Male. 68 yrs. Obese. Ambulant.

New diabetic admitted for stabilisation. Treated with oral antidiabetic drugs and diet.

OGTT not done

Fasting blood sugar on admission, 134 mg/100 ml.

	Time	Blood glucose	
		T	E
IVGTT	F	111	-
	20	166	55
	40.5	155	44
	60	144	33
k		0.36	1.28

38. J.W. Male. 49 yrs. Obese. Ambulant.

Known diabetic. Controlled with oral antidiabetic drugs and diet.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	50	-
		20	162	112
		40	150	100
		61	125	75
	k		0.65	1.11

39. B.S. Male. 62 yrs. Obese. Ambulant.

Known diabetic. Controlled with oral antidiabetic drugs and diet.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	162	-
		20	237	75
		40	225	62
		60	212	50
	k		0.33	1.04

40. B.F. Male. 80 yrs. Obese. Ambulant.

Admitted for investigation of intermittent claudication.

Known diabetic. Controlled with oral antidiabetic drugs and diet.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	66	-
		20	166	100
		40	133	67
		60	133	67
	k		0.55	1.01

41. W.McD. Male. 81 yrs. Obese. Non-ambulant.

Admitted for treatment of gross "hypostatic" leg oedema. Mild diabetes found on routine testing. Controlled with oral anti-diabetic drugs and diet.

Time		Sugar		Time		Blood glucose	
		Blood	Urine			T	E
OGTT	F	110	0	IVGTT	F	100	-
	1	210	0		20	200	100
	2	170	0		40	180	80
					60	166	66
				k		0.48	1.07

42. H.W. Male. 74 yrs. Obese. Non-ambulant.

Admitted for treatment of gangrene of the toes of one foot. Mild diabetes found on routine testing. Controlled with oral antidiabetic drugs and diet.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	84	0	IVGTT	F	83	-
	1	200	0		20	233	150
	2	164	0		40	216	133
					60	200.	117
					k	0.38	0.63

43. A.W. Male. 76 yrs. Obese. Ambulant.

Admitted for routine herniorrhaphy. Glycosuria noted on ward testing. No other diabetic symptoms. Requires insulin for adequate control but not liable to ketosis.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	128	+++	IVGTT	F	300	-
	1	190	+++		20	400	100
	2	232	+++		40	350	50
					55	325	25
					k	0.67	3.47

44. M.W. Male. 59 yrs. Obese. Ambulant.

Admitted with concussion following a road accident. Had noticed thirst and polyuria for several months previously. Requires insulin for adequate control but not liable to ketosis.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	248	+++	IVGTT	F	225	-
	1	384	+++		20	325	100
	2	396	+++		40	300	75
					61	275	50
				k		0.41	1.71

45. E.J. Female. 84 yrs. Obese. Ambulant.

Known diabetic. Controlled with oral antidiabetic drugs and diet.

	Time	Blood glucose	
OGTT not done		T	E
IVGTT	F	178	-
	20	278	100
	40	266	88
	60	211	33
k		0.69	2.75

46. P.A. Female. 55 yrs. Obese. Ambulant.

New diabetic. Glycosuria found by General Practitioner at home.

Controlled with oral antidiabetic drugs and diet.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	220	0	IVGTT	F	162	-
	1	330	++++		20	275	112
	2	310	+++		40	250	87
					60	225	62
					k	0.48	1.49

47. J.R. Female. 64 yrs. Obese. Ambulant.

Known diabetic. Controlled with oral antidiabetic drugs and diet.

OGTT not done

Time	Blood glucose	
	T	E
IVGTT F	183	-
20	333	150.
40	322	138
60	300	116
k	0.31	0.70

48. J.C. Female. 52 yrs. Obese. Ambulant.

Admitted for investigation and treatment of incipient gangrene of the left great toe. Mild diabetes found on routine testing. Treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	160	Trace	IVGTT	F	83	-
	1	340	0		20	373	290
	2	300	++++		40	350	267
					60	333	250
				k		0.32	0.42

49. J.O'T. Female. 60 yrs. Obese. Ambulant.

Admitted for tonsillectomy. Glycosuria noted on ward testing. Treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	126	0	IVGTT	F	100	-
	1	312	0		20	450	350
	2	204	0		43	350	250
					61	300	200
				k		0.99	1.38

50. S.C. Female. 71 yrs. Obese. Ambulant.

Admitted following thrombosis of the posterior inferior cerebellar artery. Glycosuria noted on ward testing. Controlled with oral antidiabetic drugs and diet.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	166	-
Fasting blood sugar on		20	333	167
admission, 156 mg/100ml.		40	300	134
		60	233	67
	k		1.01	2.50

51. M.O. Female. 49 yrs. Obese. Ambulant.

Known diabetic. Controlled with oral antidiabetic drugs and diet.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	128	0	IVGTT	F	120	-
	1	216	0		20	227	107
	2	200	0		40	210	90
					60	182	62
				k		0.59	1.50

52. M.L. Female. 76 yrs. Obese. Ambulant.

Admitted for treatment of duodenal ulcer. Glycosuria noted on ward testing. Controlled with oral antidiabetic drugs and diet.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	228	-
Fasting blood sugar on		20	370	142
admission, 264 mg/100 ml.		41	357	129
		60	342	114
	k		0.23	0.56

53. M.D. Female. 69 yrs. Obese. Ambulant.

Admitted with severe Trichomonas vaginitis and endogenous depression. Mild diabetes found on routine testing. Treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	130	0	IVGTT	F	125	-
	1	-	0		20	185	60
	2	160	0		40	175	50
					60	150	25
				k		0.28	0.91

54. M.G. Female. 64 yrs. Obese. Non-ambulant.

Admitted with vomiting and abdominal pain. Barium meal suggestive of pyloric stenosis. Condition settled with conservative measures. Glycosuria noted on ward testing. Treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	130	0	IVGTT	F	100	-
	1	236	+		20	300	200
	2	140	Trace		40	250	150
					60	150	50
					k	1.73	3.47

55. A.L. Female. 75 yrs. Obese. Non-ambulant.

Admitted for excision of multiple small epitheliomata on both legs. Glycosuria noted on ward testing. Treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	156	Trace	IVGTT	F	100	-
	1	304	0		20	200	100
	2	320	++		40	180	80
					60	170	70
					k	0.41	0.89

56. M.S. Female 72 yrs. Obese. Non-ambulant.

Admitted for treatment of ischaemic ulcer of right second toe.

Known diabetic controlled with oral antidiabetic drugs and diet.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	150	0	IVGTT	F	100	-
	1	224	0		21	200	100
	2	178	0		40	190	90
					60	180	80
					k	0.28	0.56

57. M.R. Female. 71 yrs. Obese. Ambulant.

Known diabetic. Requires insulin for adequate control but not liable to ketosis.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	190	0	IVGTT	F	100	-
	1	-	-		20	360	260
	2	340	+++		40	330	230
					60	300	200
					k	0.50	0.71

58. F.M. Female. 75 yrs. Obese. Ambulant.

Admitted for investigation of recurrent "transient cerebral ischaemic attacks". Known diabetic. Requires insulin for adequate control but not liable to ketosis.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	124	0	IVGTT	F	80	-
	1	220	0		20	140	60
	2	210	0		40	130	50
					60	120	40
				k		0.43	1.11

59. S.G. Female. 65 yrs. Obese. Ambulant.

Known diabetic. Requires insulin for adequate control but not liable to ketosis.

OGTT not done.

	Time	Blood glucose	
		T	E
IVGTT	F	124	-
	20	336	212
	40	309	185
	60	305	181
k		0.24	0.40

60. H.H. Female. 58 yrs. Obese. Ambulant.

Known diabetic. Requires insulin for adequate control but not liable to ketosis.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	211	-
		20	322	111
		42	289	78
		60	266	55
	k		0.47	1.73

61. W.G. Male. 63 yrs. Average. Ambulant.

Known diabetic with diabetic pseudo-tabes. Controlled with oral antidiabetic drugs and diet.

Time	Sugar		Time	Blood glucose	
	Blood	Urine		T	E
OGTT F	158	Trace	IVGTT F	87	-
1	230	Trace	20	225	138
2	188	+	40	212	125
			60	200	113
			k	0.29	0.50

62. M.W. Male. 39 yrs. Average. Ambulant.

New diabetic, complaining of thirst and polyuria. Admitted for stabilisation. Controlled with oral antidiabetic drugs and diet.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	125	-
Fasting blood sugar on		20	200	75
admission, 144 mg/100 ml.		40.5	195	70
		60	180	55
	k		0.26	0.77

63. S.S. Male. 57 yrs. Average. Ambulant.

Glycosuria found on routine testing while under investigation for hypertension. Diabetes controlled with oral antidiabetic drugs and diet.

Time		Sugar		Time		Blood glucose	
		Blood	Urine			T	E
OGTT	F	90	0	IVGTT	F	64	-
	1	200	++++		20	143	78
	2	180	0		41	128	64
					60	107	42
				k		0.72	1.52

64. P.M. Male. 79 yrs. Average. Non-ambulant.

Admitted for treatment of ischaemic leg pain and aneurism of the popliteal artery. GTT done as routine. Mild diabetes treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	144	0	IVGTT	F	150	-
	1	280	0		22	300	150
	2	200	0		43.5	270	120
					63	240	90
				k		0.46	1.24

65. J.B. Male. 61 yrs. Average. Non-ambulant.

Admitted following a cerebrovascular accident and embolism of the popliteal artery in the paralysed leg. GTT done as routine. Mild diabetes treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	126	0	IVGTT	F	166	-
	1	250	0		20	366	200
	2	190	0		40	350	183
					61	291	124
				k		0.56	1.16

66. T.O'C. Male. 67 yrs. Average. Non-ambulant.

Admitted for investigation and treatment of intermittent claudication. GTT done as routine. Mild diabetes treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	96	0	IVGTT	F	57	-
	1	220	0		20	186	129
	2	163	0		40	157	100
					60	132	75
				k		0.86	1.36

67. P.McC. Male. 62 yrs. Average. Ambulant.

Known diabetic. Requires insulin for adequate control but not liable to ketosis.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	270	0	IVGTT	F	187	-
	1	390	++		20	300	112
	2	320	+		40	275	87
					62	262	75
				k		0.34	0.97

68. S.W. Male. 32 yrs. Average. Ambulant.

Known diabetic. Requires insulin for control. Liable to ketosis. Admitted for re-stabilisation.

OGTT not done

	Time	Blood glucose	
		T	E
IVGTT	F	566	-
	20	766	200
	40	733	167
	61	700	134
k		0.29	0.99

69. M.H. Female. 59 yrs. Average. Ambulant.

Complained of pruritus vulvae. Glycosuria found on routine urine testing. Diabetes controlled with oral antidiabetic drugs and diet.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	186	0	IVGTT	F	162	-
	1	300	+++		20	400	238
	2	300	++++		40	350	188
					60	300	138
				k		0.72	1.37

70. S.R. Female. 45 yrs. Average. Ambulant.

Known diabetic. Requires insulin for adequate control but not liable to ketosis.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	160	0	IVGTT	F	160	-
	1	350	0		20	272	111
	2	280	0		40	244	84
					60	222	61
				k		0.51	1.49

71. G.W. Male. 65 yrs. Thin. Ambulant.

Admitted for investigation and treatment of intermittent claudication. GTT done as routine. Mild diabetes treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	102	0	IVGTT	F	110	-
	1	230	Trace		20	320	210
	2	220	+++		40	280	170
					61	271	161
				k		0.41	0.66

72. J.S. Male. 46 yrs. Thin. Ambulant.

New diabetic. Complained of thirst and polyuria. Controlled with oral antidiabetic drugs and diet.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	266	++++	IVGTT	F	200	-
	1	440	++++		21	342	142
	2	410	++++		42.5	315	115
					61	271	71
					k	0.58	1.71

73. H.W. Male. 78 yrs. Thin. Ambulant.

Known diabetic. Controlled with oral antidiabetic drugs and diet.

		Time	Blood glucose	
OGTT not done			T	E
	IVGTT	F	200	-
		25	280	80
		42	240	40
		(60	220	20)
		k	0.91	4.08

74. W.H. Male. 61 yrs. Thin. Non-ambulant.

Admitted following acute myocardial infarction. Glycosuria noted on routine ward testing. Controlled with oral anti-diabetic drugs and diet.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	160	-
Fasting blood sugar 160 mg/100 ml.		22	260	100
		47.5	250	90
		61	240	80
	k		0.20	0.55

75. J.J. Male. 65 yrs. Thin. Non-ambulant.

Admitted with chronic nephritis. Glycosuria noted on routine ward testing. Mild diabetes treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	126	0	IVGTT	F	100	-
	1	148	0		20	300	200
	2	200	0		40	250	150
					60	222	122
				k		0.75	1.24

76. J.N. Male. 65 yrs. Thin. Non-ambulant.

Admitted for investigation and treatment of intermittent claudication. GTT done as routine. Mild diabetes treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	120	0	IVGTT	F	200	-
	1	204	Trace		18.5	350	150
	2	220	++		40	330	130
					60	320	120
				k		0.22	0.54

77. F.T. Male. 70 yrs. Thin. Ambulant.

Admitted for investigation of "weak legs". No abnormality found. Known diabetic. Requires insulin for adequate control but not liable to ketosis.

	Time	Blood glucose	
		T	E
OGTT not done	IVGTT F	300	-
	20	-	-
	39	437	137
	58	412	112
	k	0.33	1.15

78. R.M. Male. 79 yrs. Thin. Ambulant.

Known diabetic. Requires insulin for adequate control. Liable to ketosis.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	233	-
		20	333	100
		40	322	89
		60	289	55
	k		0.40	1.59

79. J.L. Male. 72 yrs. Thin. Ambulant.

Admitted with a history of several "little strokes". Glycosuria found on routine ward testing. Requires insulin for adequate control. Liable to ketosis.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	300	++++	IVGTT	F	237	-
	1	540	++++		21	387	150
	2	230	++++		40	362	125
					61	337	100
				k		0.36	1.03

80. F.H. Female. 81 yrs. Thin. Non-ambulant.

Admitted for treatment of gangrene of both feet. Mild diabetes found on routine GTT. Treated with diet alone.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	92	0	IVGTT	F	92	-
	1	260	0		26	216	124
	2	200	0		40.5	191	99
					66	183	91
				k		0.39	0.74

81. R.B. Female. 26 yrs. Thin. Ambulant.

Known diabetic. Requires insulin for adequate control. Liable to ketosis.

	Time	Blood glucose	
		T	E
OGTT not done	IVGTT F	200	-
	20	325	125
	41	300	100
	60	280	80
	k	0.36	1.12

82. M.S. Female. 70 yrs. Thin. Ambulant.

New diabetic, presenting with thirst and polyuria. Requires insulin for adequate control. Liable to ketosis.

		Time	Blood glucose	
			T	E
OGTT not done.	IVGTT	F	337	-
Fasting blood sugar on		23.5	500	163
admission, 340 mg/100 ml.		40	462	125
		61	437	100
	k		0.35	1.29

83. C.W. Female. 66 yrs. Thin. Ambulant.

Known diabetic. Requires insulin for adequate control. Liable to ketosis.

		Time	Blood glucose	
			T	E
OGTT not done	IVGTT	F	228	-
		20.5	313	85
		40	300	72
		60	266	38
	k		0.42	2.04

84. J.W. Male. 63 yrs. Obese. Ambulant.

Admitted for investigation of peripheral neuritis. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	90	0	IVGTT	F	70	-
	1	144	0		20.5	140	70
	2	102	0		40	110	40
					60	100	30
				k		0.87	2.20

85. A.S. Male. 30 yrs. Obese. Ambulant.

Admitted for investigation of obesity and acne. Cushing's syndrome excluded. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	94	0	IVGTT	F	95	-
	1	132	0		20	165	70
	2	106	0		40	150	55
					60	125	30
				k		0.69	2.12

86. T.D. Male. 65 yrs. Obese. Non-ambulant.

Admitted for investigation and treatment of ischaemic leg pain.

No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	90	0	IVGTT	F	75	-
	1	180	0		20	450	375
	2	94	0		40	300	225
					62	150	75
					k	2.65	3.89

87. J.C. Male. 83 yrs. Obese. Non-ambulant.

Admitted for investigation and treatment of ischaemic leg ulcer. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	74	0	IVGTT	F	89	-
	1	126	0		20	166	77
	2	90	0		40	155	66
					61	125	36
					k	0.70	1.87

88. E.W. Female. 57 yrs. Obese. Ambulant.

Admitted for treatment of extensive psoriasis. No previous evidence for diabetes. Mother had diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	100	0	IVGTT	F	80	-
	1	140	0		24	233	153
	2	88	0		44	180	100
					60	160	80
					k	1.06	1.82

89. M.K. Female. 38 yrs. Obese. Ambulant.

Admitted for treatment of "varicose" ulcers of both legs. No previous evidence for diabetes. Mother had diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	100	0	IVGTT	F	86	-
	1	100	0		20	200	114
	2	112	0		41	166	80
					60	122	36
					k	1.23	2.85

90. A.H. Female. 50 yrs. Obese. Ambulant.

Admitted for investigation and treatment of intermittent claudication. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	98	0	IVGTT	F	110	-
	1	144	0		20	306	196
	2	116	0		40	237	127
					61	175	65
					k	1.36	2.70

91. D.L. Female. 38 yrs. Obese. Ambulant.

Admitted for investigation of "blackouts". No organic cause found. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	94	0	IVGTT	F	75	-
	1	122	0		21	210	135
	2	112	0		40	150	75
					60	110	35
					k	1.66	3.46

92. E.C. Female. 53 yrs. Obese. Non-ambulant.

Admitted for investigation and treatment of ischaemic leg ulcers. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	112	0	IVGTT	F	100	-
	1	180	0		20	275	175
	2	120	0		40	200	100
					60	150	50
				k		1.52	3.13

93. E.B. Female. 72 yrs. Obese. Non-ambulant.

Admitted for investigation and treatment of ischaemic foot ulcers. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	86	0	IVGTT	F	78	-
	1	116	0		20	187	109
	2	120	0		40	155	77
					60	137	59
				k		0.78	1.54

94. A.O'G. Female. 75 yrs. Obese. Non-ambulant.

Admitted for investigation and treatment of ischaemic pain in the foot. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	80	0	IVGTT	F	61	-
	1	110	0		21	133	72
	2	123	0		40	111	50
					60	100	39
					k	0.74	1.58

95. M.D. Female. 62 yrs. Obese. Non-ambulant.

Admitted for investigation and treatment of intermittent claudication. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	92	0	IVGTT	F	100	-
	1	176	0		20	200	100
	2	92	0		41.5	175	75
					60	150	50
					k	0.72	1.72

96. P.G. Male. 55 yrs. Average. Ambulant.

Glycosuria noted after routine herniorrhaphy operation. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	94	0	IVGTT	F	89	-
	1	128	0		20	233	144
	2	80	0		40	155	66
					(61	111	22)
					k	2.03	3.87

97. J.W. Male. 44 yrs. Average. Ambulant.

Admitted with massive angioneurotic oedema. Known to have had glycosuria for at least ten years. No other evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	62	Trace	IVGTT	F	100	-
	1	84	+		20	200	100
	2	60	++		40	140	40
					60	130	30
					k	1.08	3.01

98. J.G. Male. 61 yrs. Average. Ambulant.

Admitted for investigation and treatment of intermittent claudication. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	102	0	IVGTT	F	88	-
	1	180	0		20	222	134
	2	100	0		40	177	89
					60	133	45
					k	1.28	2.73

99. H.N. Male. 16 yrs. Average. Ambulant.

Admitted for investigation of Kleine-Levin syndrome. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	86	0	IVGTT	F	66	-
	1	120	0		20	128	62
	2	103	0		40	111	45
					60	94	28
					k	0.71	1.61

100. J.K. Male. 61 yrs. Average. Ambulant.

Admitted for investigation and treatment of intermittent claudication. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	80	0	IVGTT	F	62	-
	1	130	0		20	150	88
	2	70	0		40	137	75
					(61	75	13)
					k	0.44	0.77

101. F.M. Male. 21 yrs. Average. Ambulant.

Healthy medical student. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	119	0	IVGTT	F	87	-
	1	119	0		20	214	127
	2	88	0		40	143	56
					60	128	41
					k	1.28	2.74

102. C.D. Male. 21 yrs. Average. Ambulant.

Healthy medical student. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	88	0	IVGTT	F	87	-
	1	132	0		20	175	88
	2	90	0		40.5	117	30
					(60	81	- 6)
				k		2.13	6.01

103. W.A. Male. 21 yrs. Average. Ambulant.

Healthy medical student. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	94	0	IVGTT	F	71	-
	1	104	0		20	157	86
	2	68	0		41	117	46
					(61	85	14)
				k		1.40	3.00

104. J.McD. Male. 24 yrs. Average. Ambulant.

Admitted for investigation of hypertension. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	112	0	IVGTT	F	77	-
	1	108	0		20	215	138
	2	106	0		40	182	105
					60	155	78
				k		0.89	1.58

105. H.J. Male. 52 yrs. Average. Ambulant.

Admitted following a mild cerebrovascular accident. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	112	0	IVGTT	F	90	-
	1	154	0		20	200	110
	2	108	0		40	150	60
					60	120	30
				K		1.28	3.25

106. R.R. Male. 46 yrs. Average. Ambulant.

Admitted following a syncopal attack. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	110	0	IVGTT	F	70	-
	1	114	0		20	150	80
	2	68	0		40	110	40
					(60	80	10)
					k	1.55	3.47

107. J.L. Male. 48 yrs. Average. Ambulant.

Admitted for medical treatment of duodenal ulcer. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	98	0	IVGTT	F	70	-
	1	140	0		20	200	130
	2	88	0		41	160	90
					60	120	50
					k	1.27	2.93

108. J.C. Male. 54 yrs. Average. Ambulant.

Admitted for investigation of recurrent transient cerebral ischaemic attacks. Found to have carotid stenosis. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	94	0	IVGTT	F	80	-
	1	166	0		20	160	80
	2	108	0		40	120	40
					60	110	30
					k	0.94	2.45

109. W.H. Male. 64 yrs. Average. Non-ambulant.

Admitted for treatment of femoral artery aneurism. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	106	0	IVGTT	F	64	-
	1	128	0		20	210	146
	2	94	0		40	182	118
					60	136	72
					k	1.20	1.94

110. T.M. Male. 61 yrs. Average. Non-ambulant.

Admitted for investigation and treatment of ischaemic pain in the foot. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	102	0	IVGTT	F	86	-
	1	175	0		20	235	149
	2	100	0		40	192	106
					60	164	78
				k		1.02	1.79

111. M.O'R. Male. 65 yrs. Average. Non-ambulant.

Admitted for surgical treatment of aortic aneurism. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	116	0	IVGTT	F	75	-
	1	160	0		20	183	108
	2	120	0		40	150	75
					60	133	58
				k		0.80	1.55

112. D.S. Male. 46 yrs. Average. Non-ambulant.

Admitted during an exacerbation of chronic bronchitis. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	74	0	IVGTT	F	80	-
	1	180	0		20	260	180
	2	124	0		41	213	133
					60	173	93
					k	1.02	1.65

113. W.B. Male. 62 yrs. Average. Non-ambulant.

Admitted for investigation and treatment of intermittent claudication. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	66	0	IVGTT	F	115	-
	1	116	0		20	225	110
	2	54	0		40	190	75
					60	160	45
					k	0.85	2.23

114. A.C. Male. 73 yrs. Average. Non-ambulant.

Admitted for investigation and treatment of ischaemic pain in both feet. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	106	0	IVGTT	F	83	-
	1	180	0		20	183	100
	2	122	0		40	166	83
					60	133	50
				k		0.80	1.73

115. G.G. Female. 34 yrs. Average. Ambulant.

Admitted for investigation of low back pain. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	64	0	IVGTT	F	100	-
	1	66	0		23	211	111
	2	56	0		40	166	66
					(60	111	11)
				k		1.39	3.01

116. E.B. Female. 37 yrs. Average. Ambulant.

Admitted for treatment of disc sciatica. No previous evidence for diabetes. Had had two children with birth weights of 13 and 10+ lbs. respectively.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	86	0	IVGTT	F	78	-
	1	128	0		20	206	128
	2	124	0		40	178	100
					60	134	56
					k	1.09	2.09

117. E.D. Female. 55 yrs. Average. Ambulant.

Admitted for investigation of recurrent leg cramps. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	100	0	IVGTT	F	80	-
	1	120	0		20	200	120
	2	66	0		40	125	45
					(60	100	20)
					k	2.35	4.90

118. M.C. Female. 52 yrs. Average. Ambulant.

Under treatment for pruritus vulvae. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	100	0	IVGTT	F	75	-
	1	140	Trace		20	200	125
	2	116	0		40	150	75
					61	112	37
				k		1.41	2.95

119. M.G. Female. 56 yrs. Average. Ambulant.

Admitted for investigation of recurrent abdominal pain. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	70	0	IVGTT	F	88	-
	1	133	0		20	178	90
	2	114	0		40	122	34
					(60	111	23)
				k		1.87	4.82

120. J.F. Female. 16 yrs. Average. Ambulant.

Admitted for investigation of recurrent abdominal pain. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	86	0	IVGTT	F	83	-
	1	86	0		20	233	150
	2	96	0		40.5	183	100
					61	150	67
				k		1.08	1.98

121. J.M. Female. 21 yrs. Average. Ambulant.

Healthy medical student. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	94	0	IVGTT	F	62	-
	1	98	0		21	175	113
	2	68	0		40	106	44
					(60	75	13)
				k		2.64	5.00

122. M.T. Female. 56 yrs. Average. Ambulant.

Admitted for investigation of paraesthesiae in both feet. No organic cause found. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	96	0	IVGTT	F	100	-
	1	180	0		21	270	170
	2	114	0		40	225	125
					66.5	185	85
				k		0.83	1.52

123. A.W. Female. 49 yrs. Average. Ambulant.

Admitted for investigation of thirst and polyuria. No abnormality found. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	112	0	IVGTT	F	50	-
	1	140	0		20	225	175
	2	116	0		40	200	150
					60	150	100
				k		1.11	1.53

124. F.C. Male. 45 yrs. Thin. Ambulant.

Admitted for investigation of fainting attacks. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	92	0	IVGTT	F	66	-
	1	140	0		20	233	167
	2	94	0		40	189	122
					60	133	67
				k		1.40	2.29

125. P.C. Male. 69 yrs. Thin. Ambulant.

Admitted for amputation of the leg for severe ischaemic pain. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	92	0	IVGTT	F	100	-
	1	170	0		20	350	250
	2	124	0		42	283	183
					60	216	116
				k		1.19	1.89

126. J.M. Male. 64 yrs. Thin. Ambulant.

Admitted for treatment of ischaemic leg ulcer. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	93	0	IVGTT	F	87	-
	1	130	0		20	237	150
	2	78	0		40	187	100
					60	162	75
					k	0.88	1.78

127. C.D. Male. 54 yrs. Thin. Ambulant.

Admitted for investigation of recurrent cerebral transient ischaemic attacks. Found to have carotid stenosis. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	110	0	IVGTT	F	78	-
	1	168	0		20	178	100
	2	90	0		40	134	56
					(60	95	17)
						1.44	2.93

128. R.S. Male. 44 yrs. Thin. Ambulant.

Under treatment for pruritus ani. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	92	0	IVGTT	F	110	-
	1	104	0		20	242	132
	2	84	0		40	136	26
					(61	128	18)
					k	2.74	7.41

129. P.R. Male. 64 yrs. Thin. Ambulant.

Under treatment for disc sciatica. Found to have glycosuria on one occasion on routine testing. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	93	0	IVGTT	F	100	-
	1	120	0		20	333	233
	2	90	0		40	266	166
					60	200	100
					k	1.27	2.34

130. G.W. Male. 73 yrs. Thin. Ambulant.

Admitted for investigation and treatment of intermittent claudication. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	80	0	IVGTT	F	115	-
	1	148	0		20	425	310
	2	110	0		40	325	210
					60	275	160
				k		1.22	1.80

131. R.M. Male. 45 yrs. Thin. Ambulant.

Admitted for investigation of chronic diarrhoea. No organic cause found. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	110	0	IVGTT	F	100	-
	1	180	0		20	200	100
	2	124	0		40	150	50
					60	125	25
				k		1.44	3.47

132. J.D. Male. 73 yrs. Thin. Non-ambulant.

Admitted for investigation and treatment of ischaemic pain in both legs. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	83	0	IVGTT F		62	-
	1	153	0		20.5	169	107
	2	80	0		40.5	137	75
					60.5	112	50
				k		1.03	1.90

133. W.T. Male. 67 yrs. Thin. Non-ambulant.

Admitted for investigation and treatment of ischaemic pain in the left foot. No previous evidence for or family history of diabetes.

	Time	Sugar			Time	Blood glucose	
		Blood	Urine			T	E
OGTT	F	105	0	IVGTT F		63	-
	1	180	0		20	175	112
	2	90	0		40	150	87
					60	137	74
				k		0.60	1.02